EXHIBIT F

EpidStrategies
A DIVISION OF TOXSTRATEGIES, INC.

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I have been retained by Duane Morris LLP on behalf of the defendants to provide an expert opinion in the following case: *In Re: Valsartan, Losartan, and Irbesartan Products Liability Litigation.*, Case No. 1:19-md-02875-RBK-JS (U.S. District Court for the District of New Jersey Camden Vicinage).

In this report, I begin by describing my background and qualifications as a specialist in the field of epidemiology and listing the materials provided to me for this case. I then lay out important concepts in epidemiology that should be considered in the evaluation of epidemiologic research, including the strengths and limitations of different study designs, and types of bias. Next, I detail the literature review that I conducted according to standard and accepted methods. I then describe the key findings for each objective of the literature review, including findings of U.S. and European regulatory agencies. I conclude the report by stating my opinions in this matter.

All the opinions in this report are stated to a reasonable degree of scientific certainty. I reserve the right to supplement or amend my opinions based on any new information or literature that becomes available after this report. I further reserve the right to comment on any opinions offered by plaintiffs' proffered experts at deposition or trial. In addition, I reserve the right to discuss general concepts within the field of epidemiology to provide context for any of the opinions discussed in this report. Finally, I reserve the right to use graphics or demonstratives at trial to illustrate the concepts discussed in my report. My opinions include, but are not limited to, the following:

- Opinion 1: The scientific evidence does not support an increased risk of cancer from the low levels of N-Nitrosodimethylamine (NDMA) or N-nitrosodiethylamine (NDEA) with the use of valsartan products.
- Opinion 2: The scientific evidence does not support an association between dietary intake of NDMA or NDEA and the risk of cancer.

Background and Qualifications

I am qualified as a specialist in the field of epidemiology as it relates to pharmaceutical medication utilization and safety. I am currently Principal Epidemiologist and Practice Director of EpidStrategies, a consulting firm that specializes in epidemiology research studies. In addition, I am an Adjunct Assistant Professor at Georgetown University; an Adjunct Professor of Biostatistics at the University of Pittsburgh, Pittsburgh, Pennsylvania; and a Visiting Professor in the Department of Clinical Epidemiology at the University of Aarhus, Aarhus, Denmark.

I received my undergraduate degree in biology from Creighton University, Omaha, Nebraska, in 1985. After two years of service in rural Africa with the Peace Corps, I returned to graduate school and received my Master's degree in Public Health from the University of Michigan in 1991, and my Ph.D. degree in Epidemiologic Science from the University of Michigan in 1996. While at the University of Michigan, I received a Cancer Prevention and Control Fellowship from the National Cancer Institute.

Upon completion of my training in 1996, I joined the faculty of the University of Nebraska Medical School, where I was engaged in researching the epidemiology of cancer and other diseases. I then left to join the International Epidemiology Institute, where I conducted epidemiologic studies of pharmaceuticals, chronic diseases, and infectious diseases.

I worked in the pharmaceutical industry from 2006 to 2012. My first position was as head of Oncology Therapeutics for the Department of Epidemiology at Amgen. After three years at Amgen, I worked as head of the Oncology therapeutic area for Health Outcomes and Pharmacoeconomics at MedImmune (the biotechnical arm of AstraZeneca). In both positions, I was involved in the development of Risk Assessment Plans and Risk Evaluation and Mitigation Strategy Plans for a number of therapeutics.

I was elected a member of the American College of Epidemiology (ACE) in 2000. I also am a member of the International Society of Pharmacoepidemiology (ISPE). I serve as a reviewer of scientific papers for a number of other journals, including the *American Journal of Industrial Medicine*, *American Journal of Epidemiology*, *Annals of Epidemiology*, *BMC Public Health*, *Cancer*, *Cancer, Causes and Control*, *Cancer Epidemiology, Biomarkers and Prevention*, *Clinical Epidemiology*, *Environmental Health Perspectives*, *Epidemiology*, *Gastrointestinal Cancer: Targets and Therapy*, *International Journal of Cancer*, *Journal of Cancer Epidemiology*, *Journal of Exposure Analysis and Environmental Epidemiology*, *Journal of Medical Economics*, and *Oncology*.

I have performed studies elucidating the natural history of various diseases in support of product development and safety, including descriptive incidence studies, "real-world" disease treatment pattern studies, and co-morbidity assessments. Many of these studies have been developed to assist in the identification of early potential adverse events associated with therapeutics, and characterization of potential molecular targets for drug development.

I have taught courses and lectured at the University of Nebraska Medical Center, Georgetown University, University of Michigan, Johns Hopkins University, and University of Pittsburgh on general epidemiology, pharmacoepidemiology, and statistical methods, including the calculation and interpretation of odds ratios, risk ratios, p-values, and meta-analysis summary results to assess signal detection and causality. Further, I have more than 200 publications using these techniques.

My background and qualifications are further set forth in my *curriculum vitae*, which is attached as **Appendix A**, and includes all publications I have authored in the last ten years.

In the last four years, I have testified eleven times at deposition and two times at trial. These cases are listed in **Appendix B**.

For my work in this matter, EpidStrategies is paid $412.00 per hour.

Materials Reviewed

1. This report contains confidential material and is subject to the order governing the production, exchange, and filing of confidential information in this matter.
2. Materials I considered in forming my opinion in this report include the materials cited or referred to in this report, including:
    a. Master Personal Injury Complaint, filed June 17, 2019
    b. Consolidated Amended Class Action Complaint, filed June 17, 2019
    c. Consolidated Amended Medical Monitoring Class Action Complaint, filed June 17, 2019
    d. Plaintiffs' Disclosure of Cancer Types, filed December 31, 2020
    e. Abbreviated New Drug Application (ANDA) 204821 documents
    f. Response to DMF Information Request Letter from Zhejiang Huahai Pharmaceutical Co., Ltd (PRINSTON000012480.pdf)
    g. Health Hazard Assessments, Teva Global Patient Safety and Pharmacovigilance
        i. Valsartan Tablets, 40 MG., 80 MG., 160 MG and 320 MG, Multiple Lots, June 6, 2018
        ii. Valsartan and [Redacted-Other Product(s)] (HCTZ) tables, 80/12.5 MG., 160/12.5 MG, 160/25 MG and 320/MG, Multiple Lots, June 6, 2018
        iii. Health Hazard Assessment, Valsartan Containing Products, November 19, 2018
    h. Teva NDMA-NDEA test results
        i. TEVA-MDL2875-00063030
        ii. TEVA-MDL2875-00539061
        iii. TEVA-MDL2875-00539082
        iv. TEVA-MDL2875-00533421
        v. TEVA-MDL2875-00533423

vi. TEVA-MDL2875-00535603
vii. TEVA-MDL2875-00535609

i. Teva Tox Reports and Assessments
i. TEVA-MDL2875-00158435
ii. TEVA-MDL2875-00158440
iii. TEVA-MDL2875-00158698
iv. TEVA-MDL2875-00259857
v. TEVA-MDL2875-00259986
vi. TEVA-MDL2875-00259993
vii. TEVA-MDL2875-00260014
viii. TEVA-MDL2875-00260232
ix. TEVA-MDL2875-00260411
x. TEVA-MDL2875-00274358
xi. TEVA-MDL2875-00351418
xii. TEVA-MDL2875-00773542
xiii. TEVA-MDL2875-00953115

j. Mylan
i. MYLAN-MDL2875-00895544
ii. MYLAN-MDL2875-00029585
iii. MYLAN-MDL2875-00301525

k. FDA Documents
i. Guidance for Industry – Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches – Draft Guidance December 2008
ii. Guidance for Industry – S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use – June 2012
iii. M7(R1) Addendum to ICH M7: Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk - 9 June 2015
iv. ICH Harmonized Guidelines – Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk – M7(R1) – 31 March 2017
v. M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals To Limit Potential Carcinogenic Risk - Guidance for Industry – March 2018
vi. Combined Direct Injection N-Nitrosodimethylamine (NDMA) and N-Nitrosodiethylamine (NDEA) Impurity Assay by GC/MS, 12/11, 2018
vii. Combined Direct Injection N-Nitrosodimethylamine (NDMA), N-Nitrosodiethylamine (NDEA), N-Nitrosoethylisopropylamine (NEIPA), N-Nitrosodiisopropylamine (NDIPA), and N-Nitrosodibutylamine (NDBA) Impurity Assay by GC-MS/MS, 12/19/2019

viii. SBIA 2020 – FDA's Overview of the Guidance for Industry: Control of Nitrosamine Impurities in Human Drugs – presentation by David Keire, Ph.D., and Dongmei Lu, Ph.D. October 2, 2020
ix. Control of Nitrosamine Impurities in Human Drugs – Guidance for Industry – February 2021
x. Nitrosamines as Impurities in Drugs; Health Risk Assessment and Mitigation Workshop Day 1, March 29, 2021

l. Presentation of Dr. George Johnson, Quantitative Analysis of In Vivo Mutagenicity Dose-Response Data for Risk Assessment and Regulatory Decision-Making: A Case Study of Alkylnitrosamines
m. Plaintiff Expert Reports and CVs
i. Report of Dr. Stephen S. Hecht, Ph.D., dated July 6, 2021
ii. Report of Dr. Stephen M. Lagana, M.D., dated July 26, 2021
iii. Report of Dr. Mahyar Etminan, Pharm.D., MSc, dated July 6, 2021
iv. Report of Dr. David Madigan, Ph.D.
v. Report of Dr. Dipak Panigrahy, M.D., dated July 6, 2021

3. In addition, I reviewed the scientific literature related to risks of cancer associated with exposure to valsartan-containing medication, *N*-nitrosodimethylamine (NDMA) and *N*-nitrosodiethylamine (NDEA). This will be discussed in the next section, and a Bibliography that contains references for this literature is at the end of this report.

Introduction to Epidemiologic Study Designs

4. It is important to understand the strengths and limitations of study designs when evaluating epidemiologic studies reported in the scientific literature. Broadly speaking, there are two types of epidemiologic studies: descriptive and analytic.

Descriptive studies cannot be used to assess causality.

5. Descriptive studies, which are most often conducted on data from disease and mortality registries maintained by public health departments and government agencies, are generally used as surveillance tools to monitor the temporal trends and spatial distribution of disease or outcome occurrence. Such studies can generate hypotheses if either the temporal trends or spatial distribution shows unusual or unexpected patterns, but they cannot establish causal associations between a factor and an outcome of interest.

6. Descriptive studies include anecdotal evidence and case reports (i.e., descriptions of individuals with a particular factor or disease), which can raise suspicion that a specific factor is associated with an outcome. They are used to generate study hypotheses, not associations. Properly designed analytic epidemiologic studies need to be performed to establish associations between factors and outcomes, as discussed below. Clinical reports or case series cannot, by themselves, establish associations, let alone causality,

between the factor and the outcome, because they lack a critical element of a properly designed study—namely, a control group.

7. The inadequacy of case reports and anecdotal evidence to establish associations between putative risk factors and outcome has been recognized for many years. For example, in a well-regarded textbook, Hennekens and Buring (1987) state:

> "While case reports and case series are very useful for hypothesis formulation, they cannot be used to test for the presence of a valid statistical association. One fundamental limitation of the case report is that it is based on the experience of only one person. The presence of any risk factor, however suggestive, may simply be coincidental. Although case series are frequently sufficiently large to permit quantification of frequency of an exposure, the interpretability of such information is severely limited by the lack of an appropriate control group. This lack can either obscure a relationship or suggest an association where none actually exists." (C. H. Hennekens, Buring, Mayrent, & Doll, 1987)

<u>Analytical studies</u> are used to make causal assessments.

8. Properly designed analytic epidemiologic studies are necessary to either confirm or refute the suspicions raised by case reports or descriptive studies. Analytic studies aim to identify associations of disease with possible risk factors and to test hypotheses regarding causation. The aspect of an analytic study that enables an epidemiologist to consider causality is the use of comparison groups.

9. Randomized controlled trials are specialized epidemiologic studies in which participants are randomly (by chance) assigned to receive one of two or more clinical interventions. The "control" intervention may be the standard treatment practice, a placebo, or no treatment.

10. Randomized controlled trials are typically conducted to understand the efficacy of a treatment in relation to a comparison group. In choosing a comparison group, researchers must consider ethical standards, particularly in terms of the current standard of care. At a minimum, clinical trial patients should be offered the standard of care for their disease.

11. Because clinical trials are conducted among selected population groups with pre-specified inclusion and exclusion criteria, they cannot identify all potential adverse events in all population groups that may eventually use the treatment. Therefore, observational prospective cohort studies, defined in paragraph 15, are typically used to capture adverse-event rates.

12. The limitations to interpreting the statistical associations found in observational, nonexperimental epidemiologic studies arise largely from the fact that, for ethical

reasons, many exposures that are routinely tested on animals in the laboratory cannot be conducted on human populations. Consequently, epidemiology is largely an observational discipline, with less control over exposures than experimental studies.

13. On the other hand, experimental studies typically examine a narrow, rigidly defined range of exposures tested over a short period of time in highly selected populations; thus, the results may not be broadly applicable to real-world scenarios, making observational epidemiologic studies potentially more relevant from a public health perspective.

14. The two most used types of analytic observational studies in epidemiology are cohort studies and case-control studies. Other, less informative study designs include cross-sectional and ecologic studies.

15. Cohort studies are analytic epidemiologic studies in which defined populations are observed over time for the comparison of outcomes across risk factors. Cohort studies may be prospective, meaning that risk factors are collected in the present, prior to the outcome, and participants are followed forward in time. Alternatively, cohort studies may be retrospective, meaning that past risk-factor information is reconstructed based on existing information for participants, some or all of whom have already developed the outcome(s) or disease(s) of interest. Prospective studies, such as longitudinal cohort studies, constitute a textbook standard for supporting the validity of a causal relationship. These studies track a group of people over some period of time to examine how factors affect rates of a certain outcome. These studies are inherently time-consuming and expensive to perform.

16. Case-control studies are analytic epidemiologic studies in which individuals with the outcome of interest (cases) are compared with a suitable control group of individuals without the outcome (controls) to determine differences in risk factors between the groups. Case-control studies are typically retrospective in design, meaning that they evaluate risk factors in the past, with assessment after the outcome has occurred in cases.

17. Cohort studies measure the relative risk (RR) which is the ratio of the probability of an outcome in an exposed group to the probability of the outcome in the nonexposed group. Case-control studies measure the odds ratio (OR) which is the likelihood that the group with the outcome of interest had the exposure of interest compared to the non-diseased group (or control group). A RR or OR greater than 2 may be causal as the outcomes associated with the exposures are more likely than not due to the exposure. However, the RR or OR alone cannot determine causality without evaluation of statistical chance, bias and confounding as described further in paragraphs 18-22.

<u>The results</u> of an epidemiological study must be evaluated with respect to representativeness of the study as well as chance, bias and confounding that may

be present in a study in order to assess causality between an exposure and health outcome.

18. Epidemiological studies can be designed to measure the frequency of some disease or outcome among a population of individuals. In this instance, understanding the representativeness of the population under study is critical. It is important to understand who the study population represents in terms of person (e.g., the age, gender, and racial structure of the study population), place (e.g., the specific city, county, state, or/and country that was the setting for the study), and time (e.g., the year in which the study was conducted).

19. Statistical chance in an epidemiological study is measured so the investigator can determine how likely the observed results in a study would have occurred by chance alone if exposure was unrelated to the health outcome. Chance is evaluated with either the p-value and / or the 95 % confidence interval (95% CI). Often, p-values of < 0.05 are judged to be statistically significant, indicating that the results of the study are likely to be due to chance less than 5% of the time. The p-value is related to the study size. With a large study, a weak, or small, association with little clinical relevance might be statistically significant. However, the p-value is limited in what it can relay to the investigator. In contrast, the 95 % CI offers much more information to the investigator. It represents a range in which the true value lies with a certain degree of probability. Further, a 95% CI gives information on the direction and strength of the demonstrated effect. It must be noted that a confidence interval that contains the value of '1' indicates that the relationship between the exposure and health outcome is not statistically significant and that the results of the study could be due to chance alone.

20. When evaluating the results of epidemiological studies, it is important to assess the impact of bias on your results, to determine whether the relationship you have measured may be causal or not. One of the most important of these is selection bias, which is an error due to systematic differences between the characteristics of the people selected for a study and those who are not selected for the study. This may occur when a non-random sample of the population under study is considered. A selected group of retrospective cases are non-random samples that could potentially be affected by this type of bias.

21. Another example is confounding bias. Confounding bias is an apparent association between a disease or outcome and exposure or intervention caused by a third factor that is not considered. A confounder is a variable that is associated with the exposure or intervention and, independent of that exposure or intervention, is a risk factor for the disease.

22. Other types of information bias may affect a study. This bias includes errors in the measurement of exposures, outcomes, and confounders.

Evaluation of Epidemiological Research

Literature Review

23. I conducted a systematic literature review based on standard techniques for systematic review (PRISMA Guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009)) to identify relevant literature regarding the risks of cancer with exposure to valsartan, NDMA or NDEA:

    a. **Objective 1**. Studies that describe the risk of cancer with exposure to Valsartan pharmaceutical products.

    b. **Objective 2.** Studies that describe the risks of cancer with dietary exposure to NDMA or NDEA.

24. The following comprehensive search string was used to identify relevant epidemiologic studies in the PubMed (www.pubmed.gov) database through January 25, 2021 for Objective 1. Similar searches using equivalent terms were conducted using EMBASE (www.embase.com) and Web of Science (www.webofknowledge.com) databases to identify all relevant literature for Objective 1.

Category	Search Terms
Exposure variables	(valsartan) OR (valsartan [MeSH Terms])
Outcomes of interest	(cancer* OR tumor OR tumour OR malignan* OR neoplas*)
Filters	Humans, English

25. Because valsartan may have contained NDMA or NDEA for a period of time, the following comprehensive search string was used to identify relevant epidemiologic studies in the PubMed (www.pubmed.gov) database through January 25, 2021. Similar searches using equivalent terms were conducted using EMBASE (www.embase.com) and Web of Science (www.webofknowledge.com) databases to identify all relevant literature for objective 2.

Category	Search Terms
Exposure variables	"NDMA" OR "N-nitrosodimethylamine" OR dimethylnitrosamine OR "n-methyl-n-nitrosomethanamine" OR "n,n-dimethylnitrosamine" OR n

	nitrosodimethylamine[MeSH Terms] OR nitrosodimethylamine[MeSH Terms] OR "NDEA" OR "N-nitrosodiethylamine" OR "N,N-diethylnitrosamine" OR "diethylnitrosamine" OR n nitrosodiethylamine[MeSH Terms] OR (nitrosodiethylamine[MeSH Terms]
Outcomes of interest	(cancer* OR tumor OR tumour OR malignan* OR neoplas*)
Filters	Humans, English

26. Because studies could report on both objectives within the same article, the results of both searches were combined, de-duplicated, and reviewed together.

27. Studies were included in our systematic literature review if they had the following criteria:

    a. Study design: Observational studies (cohort, case-control, case series with n≥20)
    b. Population: Any population, no geographic restrictions
    c. Exposures:
        i. Valsartan,
        ii. NDMA synonyms: dimethylnitrosamine, nitrosodimethylamine, N¬nitrosodimethylamine, N-methyl-n-nitrosodimethylamine, N,n¬dimethylnitrosamine),
        iii. NDEA (synonyms: diethylnitrosamine, nitrosodiethylamine, N-nitrosodiethylamine, N,n-diethylnitrosamine),
    d. Comparison: Unexposed persons, or persons with less exposure
    e. Outcomes: Cancer, malignancy, tumor

28. Studies were excluded if they presented any of the criteria below:

    a. Study design: Case series with n<20, case reports, opinions, narrative reviews, editorials
    b. Population: Not human (laboratory, animal, pre-clinical study)
    c. Exposures: No exposures of interest
    d. Comparison: No comparison
    e. Outcomes: No outcomes of interest, no measures of association
    f. Other: Study not in English language.

29. After the articles were de-duplicated across objectives and databases, 1,884 articles were reviewed for relevance by title and abstract. After removing articles as defined by the inclusion and exclusion criteria, 109 articles remained. An additional 8 papers were added from reading relevant reviews, giving a total of 117 articles that were reviewed by examining the full text of the article. Among these, 25 studies were abstracted into the abstraction database. Of the 92 articles that were eliminated after reviewing the full text, 14 were eliminated because they were reviews or meta-analyses, 11 had no

exposures of interest, 27 had no outcomes of interest, 22 were opinion pieces or letters to the editor, 16 were not studies of humans, 1 study had been retracted by the publisher, and 1 was a conference abstract of an included study.

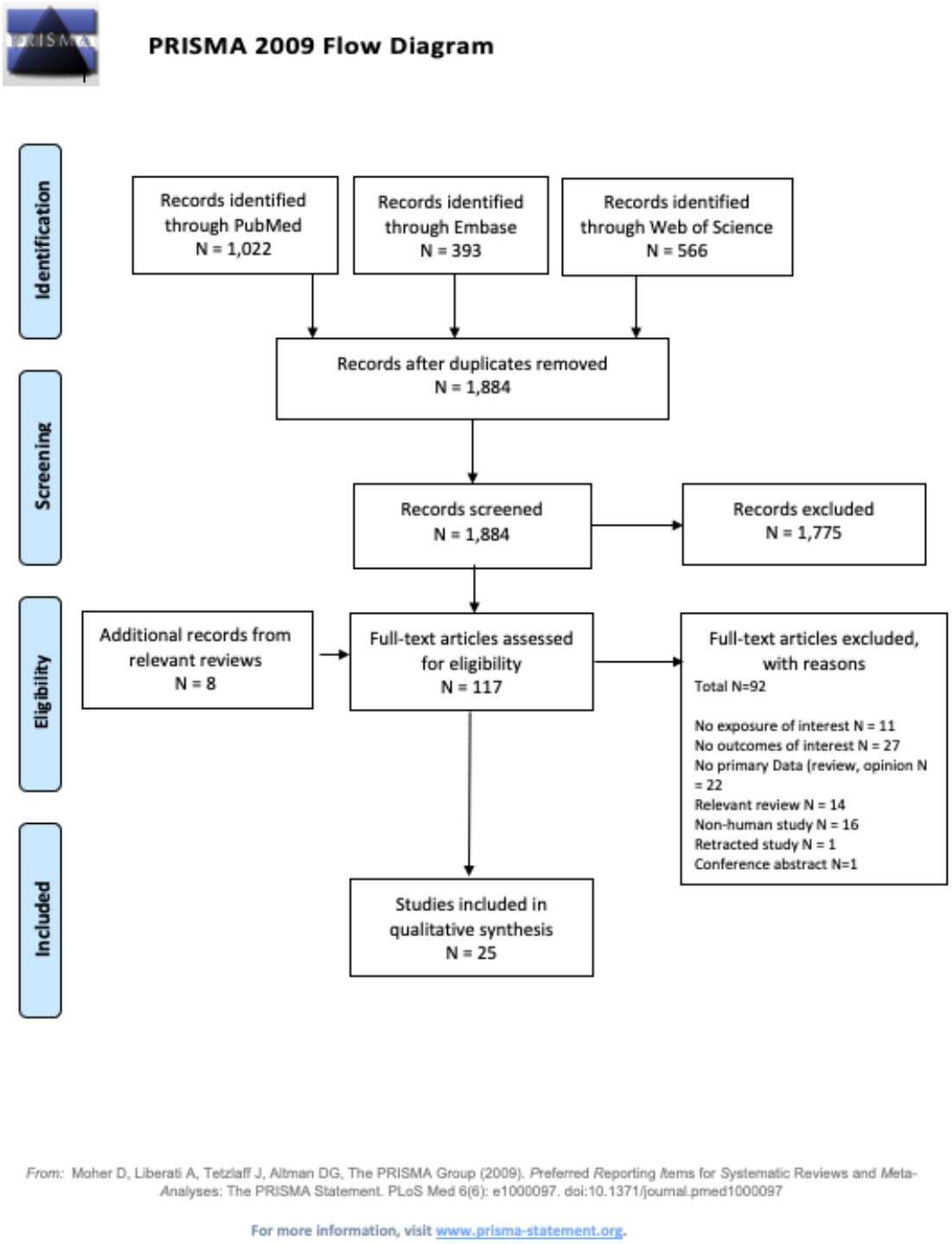


Figure 1. PRISMA flow diagram of systematic literature review results

30. Of the 25 abstracted studies, five examined the risk of cancer with specific medications that potentially contained NDMA. Two studies used the U.S. FDA Adverse Events Reporting System (FAERS), one used national registry data, and two used health insurance data. Of the studies that examined dietary NDMA or NDEA intake, six were from large cohorts such as the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, Swedish Mammography cohort, and the Netherlands Cohort study, and 14 were case-control studies.

31. The articles reviewed below contained specific information pertaining to either Objective 1 or Objective 2.

Objective 1. Studies that describe the risk of cancer with use of valsartan-containing prescriptions

<u>Valsartan and valsartan-containing prescriptions</u> are NOT associated with cancer.

32. Of the included studies, five articles described the risk of cancer with use of NDMA-containing medications, including three studies of valsartan and two studies of ranitidine.

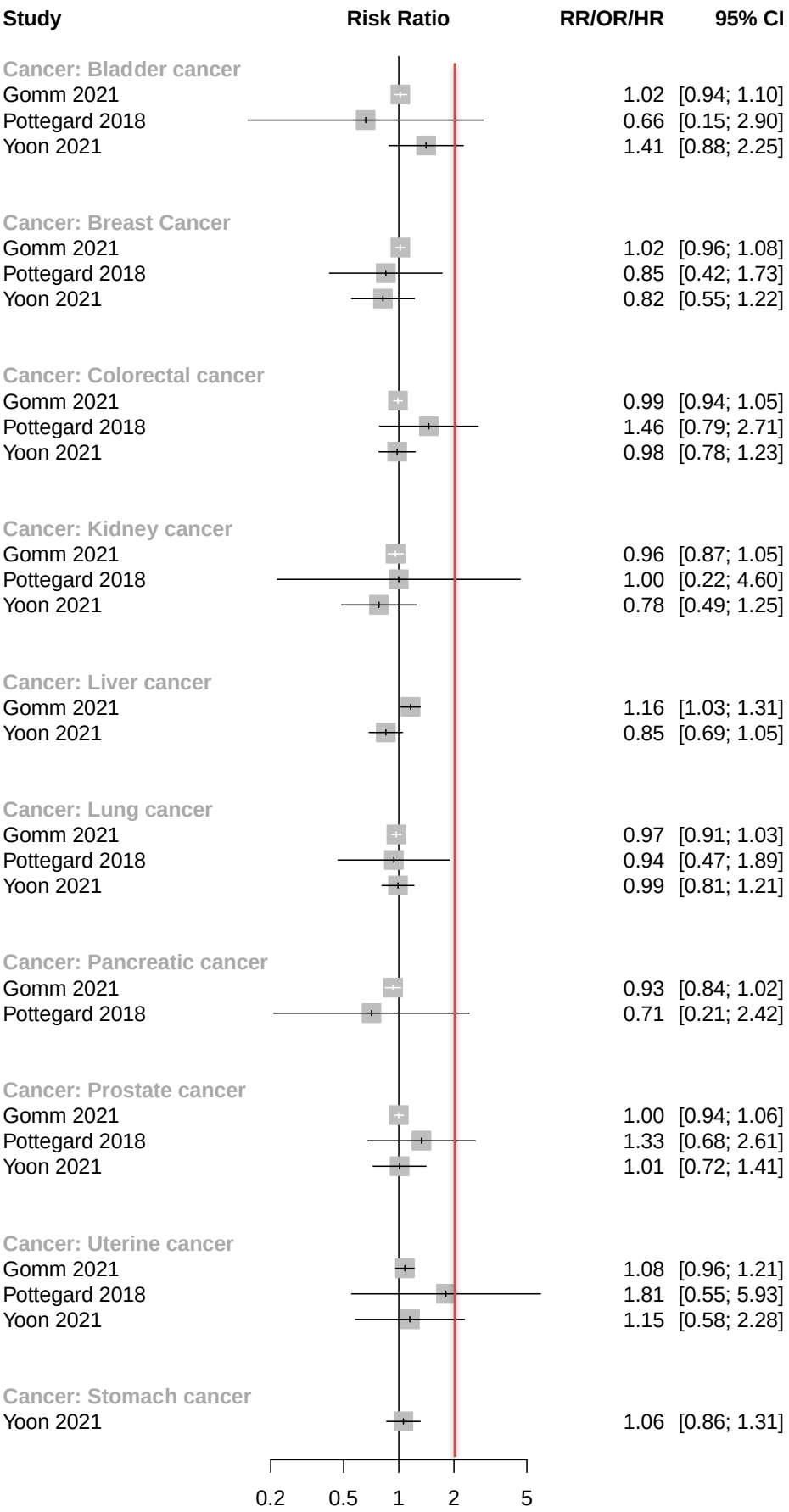


Figure 2. Studies of NDMA-containing medication and risk of cancer

33. Gomm et al. (2021) examined the risk of cancer with use of potentially NDMA-containing valsartan in Germany (Gomm et al., 2021). Data from a large German health insurance carrier was utilized to identify 780,871 patients over age 40 who filled at least one prescription for valsartan between 2012-2017. Of these patients, 409,183 were classified as ever exposed to NDMA-containing valsartan, and 371,688 were classified as never exposed to NDMA-containing valsartan, determined by the pharmaceutical registration number for filled prescriptions. Patients were followed for a median of 3.25 years. All analyses were adjusted for multiple potential confounders, including sex, age, polypharmacy (defined as prescription of five or more different drugs), prescription of low-dose acetylsalicylic acid (ASA), non-ASA non-steroidal anti-inflammatory drugs, 5α-reductase inhibitors, statins, spironolactone, glucocorticoids for systemic use, selective serotonin reuptake inhibitors, and hormone replacement therapy, diabetes, COPD, congestive heart failure, and alcohol-related diseases, the Charlson comorbidity index (score), and prevalent valsartan use. No association was found between valsartan use and overall cancer risk after adjustment for multiple confounders (HR = 1.01, 95% CI: 0.99-1.03). Valsartan prescriptions were stratified by likelihood of containing the NDMA impurity. Neither possible or probable NDMA presence was associated with a statistically significant increased risk of cancer, nor was a dose-response trend observed. Long-term use of valsartan, defined as use in at least nine quarters of the first three years of the study period, was associated with a small, non-statistically significant decreased risk of cancer (HR = 0.96, 95% CI: 0.89-1.04). Lag times of 6, 12, and 24 months did not produce any statistically significant associations. A small increased risk of hepatic cancer was observed with lag time of six months (Hazard Ratio (HR) = 1.16, 95% CI: 1.03-1.31), and similar associations with longer lag times of 12 and 24 months, as well as possible and probable NDMA exposures. At the highest dose category, valsartan containing NDMA was not associated with a statistically significant increased risk of liver cancer (HR = 1.13, 95% CI: 0.97-1.33). Long-term valsartan use was also not associated with a statistically significant increased risk of liver cancer (HR = 1.22, 95% CI: 0.80-1.89). Authors concluded that while statistical associations were reported, causality cannot be inferred from these results. Studies with longer follow-up are needed. Important liver cancer risk factors were not controlled for as well, including hepatitis B and C infections, non-alcoholic fatty liver disease, cirrhosis, obesity, heavy alcohol use, and others (American Cancer Society, 2019n).

34. In 2018, Pottegard at al. examined the risk of cancer in Danish patients prescribed valsartan that potentially contained NDMA (Pottegård et al., 2018). Four Danish national healthcare registries were utilized to identify all patients at least 40 years old who filled a valsartan prescription that likely contained NDMA. Patients with less than one year of follow-up were excluded, as well as those with a previous history of cancer except non-melanoma skin cancer. Prevalent valsartan users were defined as having filled a valsartan prescription between September-December 2011 and entered the study cohort on January 1, 2012. Incident valsartan users entered the study on the day the first valsartan prescription was filled during the study period. All subjects were

followed until cancer diagnosis or death or the end of the study on June 30, 2018. Linkage was performed with the Danish cancer and patient registries to identify all cancer diagnoses among subjects through June 2018. Individuals contributed follow-up time to the non-exposed cohort until filling their first prescription for an NDMA-containing valsartan drug. A total of 5,150 patients were included, including 3,450 who contributed person-years to the NDMA-exposed cohort, and 3,625 who contributed person-years to the unexposed cohort. The median follow-up time for the cohort was 4.6 years after applying a one-year lag period. Overall, there was no risk of cancer in the NDMA-exposed compared to the unexposed (adjusted hazard ratio (aHR) = 1.09, 95% CI: 0.85-1.41), after adjusting for confounders, including sex, age, use of low dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs, 5-α reductase inhibitors, statins, spironolactone, oral steroids, hormone replacement therapy, or selective serotonin reuptake inhibitors, history of diabetes, chronic obstructive pulmonary disease, heart failure, or alcohol related disease, Charlson comorbidity index score, and being a prevalent valsartan user. Dose response analysis by cumulative exposure to NDMA failed to show a significant trend (p-trend = 0.70). There were no statistically significant increased risks for any specific cancer diagnosis as well. Study investigators noted that, "the levels of NDMA exposure achieved through valsartan products do not translate into a substantially increased short term cancer risk."

35. An investigation into the reporting of cancer associated with valsartan prescription use was conducted using the U.S. Food and Drug Administration's Adverse Events Reporting System (FAERS) (Al-Kindi & Oliveira, 2019). Investigators identified 11,112 adverse events (AE) reported to the FDA as being associated with angiotensin-receptor blockers (ARBs) between January 1, 2017 and December 31, 2018, including valsartan (n=5,151) and other ARBs (n=5,961). A total of 14.7% of all valsartan-related AEs were for cancer, and 3.6% of other ARB reports were for cancer during the study period. The number of AEs increased at a faster rate for valsartan compared to other ARBs over the study period ($p<0.001$). Prior to the recall of valsartan products in July 2018, 5.3% of all reported ARB-related AEs were attributed to valsartan. Following the recall, this percentage increased to 23.4%. The Reporting Odds Ratio (ROR) for cancer from AEs increased from 1.7 (95% CI: 1.3-2.2) pre-recall to 7.1 (95% CI: 5.7-8.9) after the recall. A trend analysis by month revealed an abrupt increase in ROR in July 2018 (ROR = 15.4, 95% CI: 5.7-8.9) compared to the month prior to the recall (ROR = 1.8, 95% CI: 0.9-3.9). The increased ROR trend was short-lived, however. The increased reporting continued through September 2018, then declined through December (ROR = 2.9, 95% CI: 1.9-4.7), but remained above the pre-recall ROR. When stratified by consumer vs. healthcare professional reporting the AE, cancer AE reports related to ARBs reported by consumers increased dramatically in 3Q 2018, following the recall (ROR = 16.5, 95% CI: 8.0-33.7), compared to 2Q 2018 (ROR = 1.0, 95% CI: 0.4-2.7). Reports submitted by healthcare professionals also showed an increase in 3Q 2018, but not as dramatically as those reported by consumers (presented graphically only). Authors noted that the steep rise in cancer AEs related to ARBs following the recall of valsartan was biologically implausible and likely related to public alarm over the valsartan recall.

36. The FAERS website lists the uses and limitations of the data contained within its system (FDA Adverse Event Reporting System (FAERS) Public Dashboard | FDA). FAERS is described as a tool to search for adverse events reported to the FDA for drugs and biologics but is not intended to be an indicator of the safety profile of a drug or biologic. There are many limitations of the data, including duplicate and incomplete reports in the system, and unverified information in reports. The existence of a report does not indicate causation, and rates of occurrence cannot be established with reports. These results cannot be used as evidence of causation, due to the serious limitations of the AE data described by FAERS.

37. Certain lots of ranitidine were found to contain nitrosamines. Two studies in our literature search were identified that reported the risks of cancer with NDMA exposure from use of this medication. In 2020, McGwin at al. (McGwin, 2020) performed an analysis of FAERS reports for H_2 antagonists and proton pump inhibitors (PPIs) including ranitidine from 2013 through 1Q 2020. A total of 143,359 AE reports were identified related to H_2 antagonists or PPIs, 13,856 (9.8%) of which were related specifically to ranitidine monotherapy. The number of AE reports related to ranitidine as well as the total number for H_2 antagonist/PPIs increased from prior to 2013 through 1Q 2020. 0.6% of the identified AE reports occurred prior to 2013, increasing through the study period to 26.8% in 2019, then dropped in 1Q 2020 due to it only being one quarter of the year. Consumer-driven reports were the overwhelming majority of identified AE reports, compared to physicians and other health care professionals or lawyers. Consumers made 68.4% of ranitidine reports and 43.5% of H2 antagonists/PPI reports. Proportionate Reporting Ratios (PRRs) were reported for digestive system cancers for ranitidine compared to H_2 antagonists/PPIs. PRRs were statistically significantly increased for several of the cancers, including all digestive cancers (PRR = 3.66, 95% CI: 3.19-4.20) as well as cancers of the pharynx, esophagus, stomach, colorectal, liver and pancreas. Cancer of the mouth, anus, and gallbladder had non-statistically significant increased PRRs. These results have the same limitations as the study by Al-Kindi with the use of FAERS data and should be interpreted with caution. FAERS data cannot support causation due to the nature of its self-reported, unverified data.

38. The second study of ranitidine and risk of cancer was a nationwide cohort study in South Korea (Yoon, Kim, Seo, & Park, 2021). A national insurance claims database was used to identify patients prescribed ranitidine for more than one year with cumulative doses above 10,800 mg between 2009 – 2011. The database was also used to match patients prescribed famotidine, an H_2 antagonist similar to ranitidine that did not contain NDMA. Patients had to have used famotidine for more than one year with cumulative doses above 14,400 mg during the same period and were matched to cases by age, sex, diabetes, and cumulative exposure to the cases in a ratio of 4:1. Those who used either drug in 2007 - 2008, had overlapping use of both drugs during 2009-2011, were diagnosed with cancer between 2007-2011, were under 30 or over 80 years old, or died before December 2011 were excluded. A total of 40,488 ranitidine users and 10,122 famotidine users were included in analyses. Hazard ratios for 11 cancer

outcomes between 2012 – 2018 were calculated. There was no statistically significant difference in all cancer risk between ranitidine and famotidine users (HR = 0.99, 95% CI: 0.91-1.07). Additionally, there was no statistically significant difference between the groups in any of the 11 specific cancer outcomes. Analysis by cumulative duration of intake showed no difference in the overall cancer risk between the groups (p=0.72), nor for any specific cancer outcome. No association between probable NDMA exposure through ranitidine and short-term risk of cancer was observed. The follow-up period was seven years; it was acknowledged that further research is needed to assess long-term cancer risk.

39. My review of cohort studies of people who used medications that potentially included NDMA showed that there was no increase in overall cancer in any of the studies. While a slight increase of liver cancer in one German study of valsartan users (Gomm et al, 2021) was found, this was not supported by a study of Danish valsartan users (Pottegård et al, 2018) and South Korean ranitidine users (Yoon et al., 2021). The two studies that observed increased reporting of cancer with valsartan use (Al-Kindi & Oliveira, 2019) or ranitidine use (McGwin, 2020) were based on unverified, self-reported data from the U.S. FDA FAERS data system that that cannot be used to infer causation. Each of these studies of cancer risk with NDMA-containing medications based on FAERS data had several limitations that prevented the determination of causation. Our systematic literature search did not identify any studies which examined the risk of cancer with medications that may contain NDEA.

40. Figure 2 shows that all risk estimates are less than 2 indicating that there is no relationship between NDMA-containing medications and cancer.

Objective 2. Studies that describe the risk of cancer with intake of NDMA or NDEA through diet

<u>Cancer is not consistently and reliably associated with NDMA or NDEA</u> through diet in the medical literature.

41. Of the studies that evaluated risk of cancer with intake of NDMA or NDEA through diet, there were six cohort studies and 14 case-control studies.

Food frequency questionnaires (FFQ) are extremely limited in the information they provide and findings from them must be interpreted with caution.

42. One critical consideration for these studies is that NDMA and NDEA intake levels from food are generally determined from food frequency questionnaires (FFQ). Food frequency questionnaires include a list of foods (or groups of foods) and beverages with a response section for respondents to indicate how often they eat or drink each food or beverage. Some food frequency questionnaires include portion sizes (semi-quantitative) while others do not (non-quantitative). Nutrient intake is calculated by multiplying the frequency of consumption of each food by the amount of nutrient in a serving of that food using reference databases. The advantages of the food frequency

questionnaire are that it is generally representative of foods eaten habitually and measurement of foods with high day-to-day variability can be captured accurately. Disadvantages include that it is a retrospective method that relies on respondent memory and that the list of foods included is not all-encompassing, especially for foods specific to certain ethnic groups. Further, changes in dietary habits over time can't be considered. Finally, it must be noted that the resulting nutrient intakes from a food frequency questionnaire are meant to rank individuals according to intake rather than serve as absolute measures of intake.

43. Because FFQs are self-reported, they are particularly susceptible to misclassification bias. Study participants give responses to these types of questionnaires to make themselves look as good as possible, so will under- or overestimate certain behaviors. For example, in a study of obesity and mortality, the differences between self-reported BMI compared to actual measurements caused 20% of subjects to be miscategorized (Preston, Fishman, & Stokes, 2015). While FFQs are generally representative of dietary habits, in case-control studies of chronic diseases such as cancer, nutrient intake 10-20 years prior to disease would be more relevant to capture diet habits prior to cancer development. Information this far in the past is difficult to assess accurately. Studies of dietary NDMA intake summarized here generally gathered data on dietary habits in the past year. Case-control studies examine past exposures of participants that have disease currently, by design. These studies are susceptible to recall bias because those with disease are likely to remember past exposures differently than control subjects. Observed results from these studies would not reflect the true effect of the exposure (C. H. Hennekens, Buring, J.F., 1987). Cohort studies, on the other hand, measure exposures at entry into the study and prior to disease development, so are likely to be more accurate but still would not capture changes in diet over time.

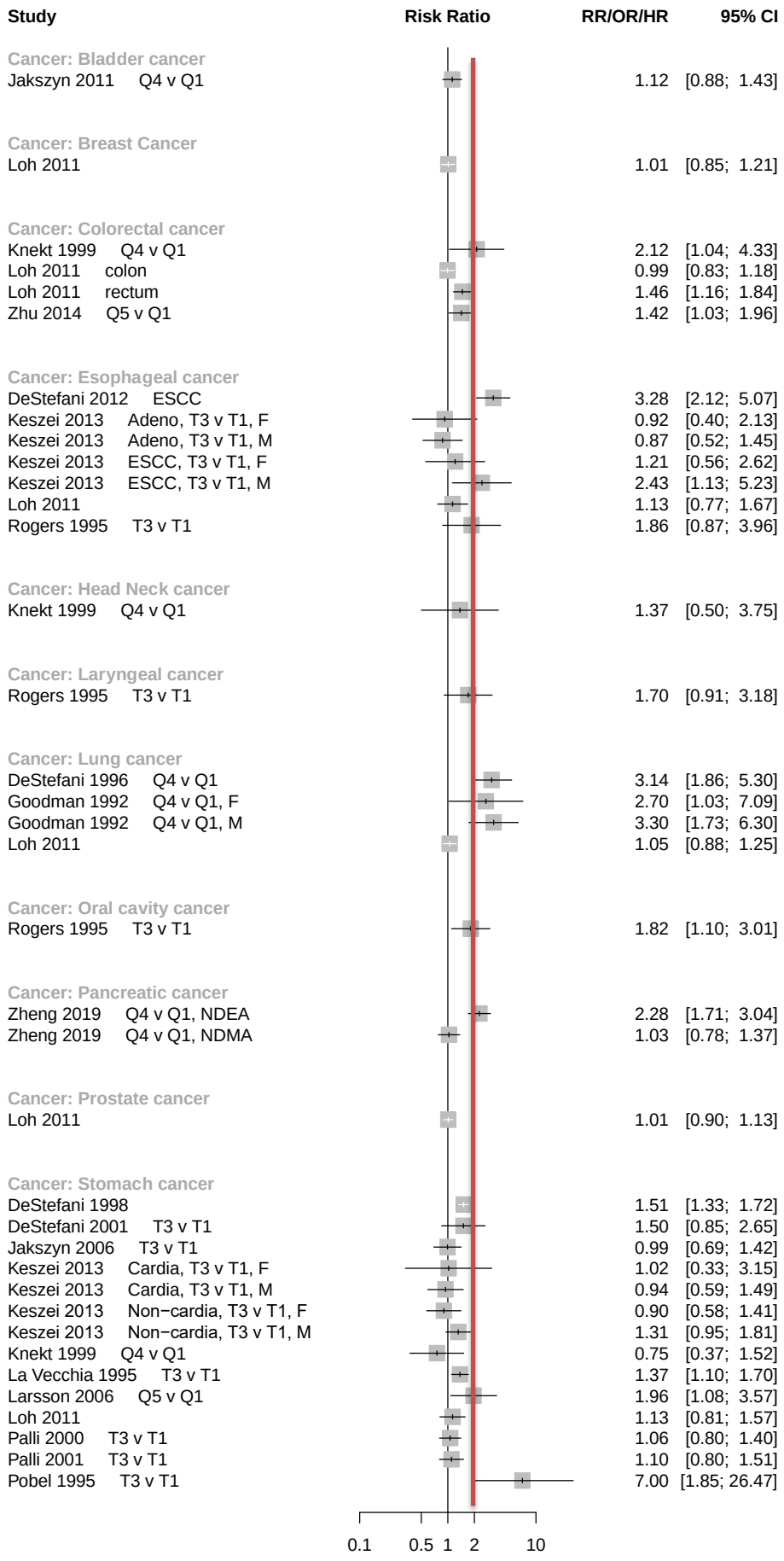


Figure 3. Studies of NDMA or NDEA dietary intake and risk of cancer

<u>Cohort studies have not demonstrated</u> that NDMA or NDEA in diet are associated with any cancer type.

44. Of the included articles, six large prospective cohort studies reported data on the risk of cancer with exposure to NDMA, and none reported the risk of cancer with NDEA.

45. Knekt at al.(1999) examined the risk of colorectal and other gastrointestinal cancers with exposure to n-nitroso compounds in a cohort of 9,985 Finnish adults that was followed for up to 24 years (Knekt, Järvinen, Dich, & Hakulinen, 1999). Between 1966-1972, screening examinations were conducted in several regions of Finland, including collection of data on detailed food consumption in the past year as well as smoking habits. Mean daily NDMA intake from the diet was 0.052 μg and specifically from beer was estimated in a subgroup as 0.071 μg. Cancer diagnoses were obtained from the Finnish Cancer Registry from 1967 through 1990 and evaluated by quartile of NDMA exposure. The risk of head and neck cancer decreased with increasing level of NDMA intake with the highest level of NDMA conferring the lowest non-statistically significant risk (aRR=1.37; 95% CI=0.50-3.74). Further, there was no dose-response trend observed (p=0.43). There were no statistically significant risks of stomach cancer in any quartile measured and the highest quartile had the lowest nonsignificant risk (Q4 aRR = 0.75, 95% CI: 0.37-1.51, p-trend=0.39). An increased risk of colorectal cancer was observed in the highest quartile of NDMA intake compared to the lowest (Q4 aRR = 2.12, 95% CI: 1.04-4.33), but not in the lower two quartiles, and there was no dose-response trend (p=0.47). All RRs were adjusted for sex, age, municipality, smoking and energy intake. While the association between NDMA and colorectal cancer observed in this study is plausible, the authors state that confounding cannot be ruled out. The association seen may be due to some unmeasured dietary or life-style habits related to development of the disease.

46. In 2006, Jakszyn at al. reported on gastric cancer risk with exposure to n-nitroso compounds in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort (Jakszyn et al., 2006). The EPIC cohort consisted of over 500,000 subjects from 10 European countries aged 35-70 years and recruited between 1992 and 1998. Follow-up was conducted with population cancer registries. Usual diet over the past 12 months and lifestyle information was collected at baseline via questionnaire. NDMA intake was then estimated by matching food items to a food database. The estimated geometric mean for NDMA was 0.114 μg per day. A total of 314 incident gastric cancer cases (92 cardia, 155 non-cardia) were identified in this cohort. A non-significant decreased risk of stomach cancer was observed by tertile of endogenous NDMA exposure (T2 HR = 0.87, 95% CI: 0.64-1.2; T3 HR = 0.99, 95% CI: 0.69-1.41, p-trend = 0.96) after adjusting for potential confounders. Cardia stomach cancer had similar decreased risks with NDMA intake. Non-cardia stomach cancer had increased risks with tertiles of NDMA, but none were statistically significant. When analyzed continuously, dietary NDMA was not associated with an increased risk of gastric cancer (HR = 1.0, 95% CI: 0.70-1.43 per 1 μg increase in NDMA). Neither cardia nor non-cardia gastric cancers were associated with a statistically significant increased risk with NDMA.

47. Another study of stomach cancer risk with dietary nitrosamine consumption was conducted in women enrolled in the Swedish Mammography Cohort (Larsson, Bergkvist, & Wolk, 2006). This cohort enrolled women between 1987-1990 who had been born between 1914 - 1948 and resided in two counties in central Sweden. Women completed a questionnaire on diet, alcohol use, weight, height, and education at baseline and up to ten years later in 1997. Cohort members with implausible food values and those with a previous cancer diagnosis were excluded, leaving 61,433 women for the current study. NDMA intake was assessed with the food frequency questionnaires (FFQ) at baseline and a FFQ in 1997 of items consumed in the previous year and matched to tables of nutrients in Swedish foods in the 1980s. Foods included in the NDMA values included processed meat products, smoked fish, caviar, roe, alcoholic beverages (beer and whiskey) and chocolate. National and regional cancer registries were used to obtain cancer diagnoses through 2004. 156 incident stomach cancer cases were identified in the cohort. In multivariate models, there was a trend of increasing risk of stomach cancer with increasing NDMA intake and a dose-response trend was observed (p-trend = 0.02). Analyses were also performed for specific food items. Increasing intake of both total processed meat (T3 HR = 1.66, 95% CI: 1.13-2.45, p-trend = 0.01) and bacon/side pork (T3 HR = 1.55, 95% CI: 1.00-2.41, p-trend = 0.05) were associated with an increased risk of stomach cancer. However, only the highest levels of intake had statistically significant increased risks. Other processed meats such as sausage/hot dogs, ham/salami, and other food items such as total red meat, poultry or fish intake were not associated with statistically significant increased stomach cancer risks at any intake levels.

48. The EPIC cohort was also used to examine the risk of bladder cancer with dietary nitrosamine intake (Jakszyn et al., 2011). As described above, EPIC is a large cohort study involving a half million Europeans with data on diet and lifestyle. After a mean follow-up of 8.7 years, 1,001 bladder cancer cases were identified in the cohort. In multivariate models, the risk for bladder cancer at the highest level of NDMA intake (0.19 – 21.11 µg/day) was not statistically significant (HR = 1.12, 95% CI: 0.88-1.44). Analyzed as a continuous variable, there was a non-significant decreased risk per unit increase in NDMA intake (HR = 0.98, 95% CI: 0.92-1.05). There were no statistically significant associations with NDMA intake when stratified by high- and low-risk bladder cancers, smoking, gender, or high vs low exposure occupations.

49. A study that examined the risk of cancer with dietary n-nitroso compounds was conducted in a regional subset of the EPIC cohort (Loh et al., 2011). The EPIC-Norfolk cohort includes over 23,000 adults aged 40-79 years old, recruited between 1993 and 1997 and residing in Norfolk, UK. Dietary and lifestyle data was collected by means of a questionnaire at baseline. Physical examinations were also conducted to gather anthropometric measures, respiratory functions, and blood pressure data. Dietary NDMA was estimated by a baseline FFQ matched with a food database of NDMA concentrations. After a mean follow-up of 11.4 years, a total of 3,268 cancer diagnoses were identified through June 2008 using the East Anglican Cancer Registry. Mean NDMA levels were 59.1 ng/day (0.059 µg/day) for cancer cases, and 57.0 ng/day

(0.057 µg/day) for non-cases. The risk of all cancer by quartiles of NDMA intake did not show any statistically significant associations after adjusting for potential confounders such as age, sex, BMI, cigarette smoking status, alcohol intake, energy intake, physical activity, educational level, and menopausal status (in women). At the highest quartile of intake (mean 0.125 µg/day), the HR for all cancer was 1.10 (95% CI: 0.97-1.24), when fully adjusted. Stratification by gender revealed a significant association in men in the highest quartile, but not women. When NDMA intake was analyzed as a continuous variable, there was a small statistically significant increased cancer risk per unit increase in NDMA intake in the full study population (HR = 1.06, 95% CI: 1.01-1.12), as well as in men (HR = 1.09, 95% CI: 1.03-1.16), but not in women (HR = 1.05, 95% CI: 0.96-1.16). Intake of a high level of vitamin C (≥50 µmol/L) attenuated the result for all cancer slightly, and significance was lost (HR = 1.01, 95% CI: 0.94-1.10). NDMA as a continuous variable was also analyzed for specific cancer sites, with no significant associations observed except with rectal cancer (HR = 1.46, 95% CI: 1.16-1.84), GI cancers (HR = 1.13, 95% CI: 1.00-1.28), and other cancers (HR = 1.11, 95% CI: 1.03-1.19). Authors noted the limitations such as biases in measurement error associated with using FFQs for dietary assessments, and multiple risk factors that are not controlled in analyses for the specific cancers examined.

50. Keszei at al. examined the risk of esophageal and gastric cancers with dietary n-nitroso compound intake using the Netherlands Cohort Study (Keszei, Goldbohm, Schouten, Jakszyn, & van den Brandt, 2013). The Netherlands Cohort Study is comprised of over 120,000 Dutch residents ages 55-69 years old that were recruited in 1986, selected as a sample from population registries by sex-stratified random sampling. During the 14.3 years of follow-up, 924 cancer cases were identified through record linkage with the Netherlands Cancer Registry and National Network and Registry of Histo- and Cytopathology. A random subset of 5,000 participants were selected for comparison. After exclusions for prevalent cancer and incomplete/inconsistent dietary data, 4,032 participants remained in the comparison group. A questionnaire was administered at baseline to collect information on dietary habits and other risk factors for cancer. NDMA intake was estimated from the baseline FFQ matched to published measures of NDMA in Dutch foods and analyzed as tertiles. Median NDMA was much higher for men (0.08 µg/day) than women (0.04 µg/day). 73% of NDMA intake was from beer and processed meat. In men, esophageal squamous cell cancer was associated with NDMA intake (T3 HR = 2.43, 95% CI: 1.13-5.23, p-trend=0.01), but not for women (p-trend = 0.57). Analyzed as a continuous variable, esophageal squamous cell cancer risk was increased per unit increase of NDMA for both men (HR = 1.15, 95% CI: 1.05-1.25) and women (HR = 1.34, 95% CI: 1.04-1.71). Conversely, NDMA was not associated with a statistically significant increased risk of esophageal adenocarcinoma or gastric cardia adenocarcinoma, analyzed as a categorical or continuous variable. Risk of gastric non-cardia adenocarcinoma was statistically significantly increased with NDMA intake, but only when analyzed as a continuous variable, and only in men (HR = 1.06 per unit NDMA increase, 95% CI: 1.01-1.10). Limitations include those inherent to studies of nutrition. FFQs were used at baseline to assess diet across the

whole study period with the assumption that diet doesn't change over time. Further FFQs are prone to misclassification of dietary intake.

Case-control studies assessed as a whole have not found strong evidence that NDMA or NDEA are associated with cancer.

51. Of the included articles, 14 case-control studies reported data on the risk of various cancers with exposure to NDMA, including one study that also reported the risk of cancer with NDEA.

Lung Cancer

52. Two case-control studies reported risk of lung cancer with dietary NDMA intake. The first was a case-control study of high fat foods and lung cancer conducted in Hawaii (Goodman, Hankin, Wilkens, & Kolonel, 1992). Between 1983 and 1985, 326 histologically confirmed cases of lung cancer between ages 30-84 were identified in any of the seven major civilian hospitals on Oahu. Population-based controls (n=865) were matched to cases 2:1 on sex and 5-year age group. Interviews for all subjects were conducted for information on diet history, vitamin use, tobacco history, and other demographic and anthropometric data. Proxy interviews with spouse or next-of-kin were conducted for 29% of cases and 7% of controls if the subject had died or was too ill to participate. Subjects who smoked pipes or cigars exclusively were excluded from analyses, as well as those with incomplete smoking histories. An association between NDMA and risk of lung cancer was observed for men in the highest two categories of NDMA intake (Q3 OR = 2.8, 95% CI: 1.4-5.3, Q4 OR = 3.3, 95% CI: 1.7-6.2) with a strong dose-response trend (p-trend = 0.0006) after adjusting for age, ethnicity, smoking status, pack-years of cigarette use, and beta-carotene intake. In women, the observed association was not as strong as for men (Q4 OR = 2.7, 95% CI: 1.0-6.9, p-trend = 0.04). Sporadic associations were observed with intake of specific foods high in NDMA after adjusting for confounders. In men, associations were seen with processed meats including luncheon meat, bacon, and sausage, but not ham, bologna, or spam. In women, only the second highest levels of luncheon meat and the highest intake of bacon were associated with a statistically significant increased risk of lung cancer. The large percentage of proxy interviews in the cases may have introduced misclassification bias if the next-of-kin or spouse did not complete the interview with accurate information on the case.

53. The second study of lung cancer was conducted by DeStefani in Uruguay (De Stefani, Deneo-Pellegrini, Carzoglio, Ronco, & Mendilaharsu, 1996). Between May 1994 and December 1995, 320 cases of lung cancer admitted to any of the four hospitals in Montevideo, Uruguay were identified and frequency-matched on age, sex, and residence 1:1 to hospital controls who had been admitted for diseases unrelated to tobacco use. All subjects underwent interviews that included demographics, tobacco history, alcoholic and non-alcoholic beverage consumption, and a FFQ. NDMA intake was estimated by matching the FFQ to a local conversion table and categorized into

quartiles. An association was seen between NDMA intake and lung cancer at the third (OR = 1.77, 95% CI: 1.06-2.96) and highest quartiles (OR = 3.14, 95% CI: 1.86-5.29) of intake, controlling for age, sex, residence, urban/rural status, family history of lung cancer, BMI, pack-years, and total energy intake. Compared to non-smokers in the study, current smokers had a 9-fold risk of lung cancer (OR = 9.1, 95% CI: 5.2-15.9). When analyses were stratified by this strong confounder, statistically significant increased risks were found only in current smokers with the highest 2 quartiles of NDMA intake (Q3 OR = 2.0, 95% CI: 1.07-3.82, Q4 OR = 2.95, 95% CI: 1.53-5.64), while nonsmokers and former smokers had non-statistically significant increased risks with NDMA intake. Lastly, risk of lung cancer with intake of different NDMA-containing foods revealed statistically significant increased risks for salted meat only (OR = 1.56, 95% CI: 1.01-2.42), which had the highest estimated NDMA concentration (2.30 µg/kg). None of the other 12 foods examined were associated with an increased risk of lung cancer.

54. While the two case-control studies described above saw a risk between higher levels of NDMA and lung cancer, a prospective cohort study (Loh, 2011) did not. In cohort studies, one measures the exposure (ie., diet) prior to the development of disease while in case-control studies, exposure is measured retrospectively, after the disease has developed. To this end, cohort studies are less susceptible to recall or information bias in exposure assessment than case-control studies. Therefore, it is likely that some level of recall bias existed in the case-control studies which lead to the increased lung cancer risk finding. For example, Loh et al. (2011) conducted a prospective cohort study and measured diet between 1993 and 1997 (before cancer was diagnosed) while incident cancer was ascertained up to 15 years later. In contrast, the two case control studies ascertained diet at the time of the diagnosis of lung cancer for the cases. De Stefani (1996) asked lung cancer cases (and their controls) to recall their diet 5 years prior to diagnosis while Goodman (1992) asked them to recall their diet 1 year prior to diagnosis. Cancer cases are more likely to recall their diet differently than controls as they are newly diagnosed with cancer and are, at this point in their disease, trying to remember what may have caused their disease.

Stomach Cancer

55. NDMA intake and stomach cancer risk has been studied extensively. In addition to the cohort studies above that reported results for stomach cancer risk, eight case-control studies and a meta-analysis were identified. The earliest study was conducted By Risch and colleagues in Canada of dietary factors and stomach cancer (Risch et al., 1985). A total of 246 cases of stomach cancer in 35-79 year-old residents of Newfoundland, Manitoba or Toronto, Ontario were identified through provincial tumor registries and hospital records. Population controls were identified by random door-to-door contact assisted by provincial electoral lists and matched to cases 1:1 on sex, birth year (within 4 years) and residence, with further matching on neighborhood in Manitoba and Newfoundland. All subjects completed questionnaires, including an FFQ of dietary patterns in the previous year which were matched to food composition tables. A non-

statistically significant decreased risk in stomach cancer was observed for every 10 µg/day increase (OR = 0.94, 95% CI: 0.14-6.13). However, stomach cancer risk was increased with increasing smoked meat intake, a food high in NDMA (OR = 3.92 per 100g/day, 95% CI: 1.76-8.75), after adjusting for other food groups, total food consumption and ethnicity. Authors noted that the case response rate was low (44%) and 1/3 of cases were excluded due to death or severe illness, so the included cases may represent earlier or less severe form of the disease.

56. Gonzalez at al. examined the risk of stomach cancer with nutritional factors in Spain. Between 1988-1989, 354 cases of histologically-confirmed cases of stomach cancer were identified in four regions of Spain. Hospital controls were matched to cases 1:1 on age, sex, and residence, and had been admitted for diseases unrelated to diet. All participants completed interviews, including a questionnaire on dietary patterns in the previous 12 months preceding the onset of illness. A conversion table was used to estimate the energy and nutrient intakes. Median NDMA in cases was 0.18 ng/day and 0.16 ng/day in controls. An increasing risk of stomach cancer was seen with increasing NDMA intake, with ORs for quartiles 2, 3 and 4 reported as 1.86, 1.79, and 2.09, respectively (p-trend = 0.007). When stratified by histologic type, both intestinal and diffuse types had increased risks with all NDMA intake levels, but no confidence intervals were reported, so the significance of these increased risks is unknown. Neither intestinal (p-trend 0.101) or diffuse (p-trend = 0.133) stomach cancer showed a dose-response trend. High NDMA intake paired with low vitamin C intake increased the risk of stomach cancer (OR = 1.98, 95% CI: 1.28-3.08) compared to low intake of both NDMA and vitamin C. High intake of vitamin C appeared to mitigate the effect of high NDMA intake (OR = 1.17, 95% CI: 0.74-1.85). Authors cautioned that NDMA concentrations depend on environmental factors and can have a wide variation for the same food.

57. In a case-control study in Milan, Italy, LaVecchia and colleagues identified 746 incident stomach cancer cases between 19-74 years old diagnosed between 1985 - 1993, and 2,053 unmatched controls from the same hospitals admitted for non-cancer, non-digestive tract diseases (La Vecchia, D'Avanzo, Airoldi, Braga, & Decarli, 1995). A questionnaire administered to all subjects collected information on demographics, anthropometrics, smoking, alcohol intake, intake of coffee or other methylxanthine-containing beverages, medial history, family history of selected cancers, reproductive factors and an FFQ. NDMA values were estimated from matching the FFQ to an Italian survey of selected foods or other published data. The mean daily NDMA intake for this population was 0.18 µg/day. Using the fully adjusted model, there was an increased risk of stomach cancer at the highest intake of NDMA ($\geq$ 0.191 µg/day) (OR = 1.37, 95% CI: 1.1-1.7), but not the middle tertile of intake (OR = 1.11, 95% CI: 0.9-1.4). However, a dose-response trend was observed ($p<0.01$). Stratified by gender, this increased risk was seen only in men and not women. Authors noted the limitations of not having measurements of nitrosamine concentrations in drinking water, or measures of endogenous N-nitroso compound formation, which is influenced by several

individual factors such as gastric pH levels, microbial species in the mouth and stomach, N-nitrosation inhibitors, and subjective individual variation.

58. A study of French stomach cancer cases and matched controls was conducted by Pobel and colleagues (Pobel, Riboli, Cornée, Hémon, & Guyader, 1995). Between 1985 and 1988, 92 cases of histologically confirmed cases and 128 non-cancer controls matched on sex and age were included. Interviews collected data on demographics, socioeconomic status, occupation, medical history, family history of cancer, tobacco, and alcohol consumption. A dietary history questionnaire was included on habits in the past year, and answers were matched to a food value table and published data for NDMA values. Median daily NDMA intake was 0.25 µg/day for cases, which was statistically significantly higher than that of the controls (0.23 µg/day, $p<0.01$). There was a 7-fold risk of stomach cancer with the highest NDMA intake (OR = 7.00, 95% CI: 1.85-26.46), and a non-significant increased risk in the middle tertile (OR = 4.13, 95% CI: 0.93-18.27). A dose-response trend was observed when NDMA was analyzed as a continuous variable (p-trend = 0.04). Results were adjusted for age, sex, occupation, and total caloric intake.

59. Two case-control studies of stomach cancer and nitrosamines were conducted in Uruguay by the same authors. From 1993 - 1996, 340 cases of stomach cancer were identified, along with 698 hospital-based controls that did not have conditions related to the digestive tract, nutritional disorders, tobacco or alcohol use (De Stefani, Boffetta, Mendilaharsu, Carzoglio, & Deneo-Pellegrini, 1998). Controls were frequency-matched to cases on age, sex and residence. All subjects were interviewed for sociodemographic, tobacco, alcohol information and a limited FFQ that did not allow for total energy intake calculations. The NDMA intake was estimated by matching the FFQ to food table values for fried, boiled, or salted meat. NDMA intake in the study population ranged from $\leq$0.14 - $\geq$0.27 µg/day. NDMA intake was found to be associated with an increased risk of stomach cancer (OR = 1.51, 95% CI: 1.33-1.72, p-trend <0.001) overall, after adjusting for age, gender, residence, urban/rural status, smoking, alcohol, and maté consumption. When stratified by gender, men had a slightly higher risk (OR = 1.63, 95% CI: 1.39-1.91) than women (OR = 1.34, 95% CI: 1.08-1.67). By category of exposure, the risk of gastric cancer was increased at all intake levels (p-trend<0.001). Measured continuously and included in a single model with other food items and micronutrients, increasing NDMA intake was associated with increased risk of stomach cancer (OR = 1.58, 95% CI: 1.25-2.00)

60. Because the previous study used a limited FFQ that did not allow for the estimation of total energy intake, a new study was conducted to better assess the relationship between meat (and related nutrients and bioactive substances) and stomach cancer (De Stefani, Ronco, Brennan, & Boffetta, 2001). Between September 1997 and August 1999, 123 cases of stomach cancer were identified in the four major hospitals of Montevideo, Uruguay, and 264 hospital-based controls, using the same methods as previously. Data collection was improved with the use of a more robust FFQ that allowed for calculation of total calorie intake. With the updated FFQ, intake of NDMA in this population was

much higher than other published diet studies, ranged from ≤1.9 - >2.6 µg/day. After adjusting for age, gender, residence, urban/rural status, tobacco smoking, alcohol drinking, maté drinking, total energy, protein, and total fat, there was no statistically significant association between NDMA intake at any level and gastric cancer risk (T3 OR = 1.5, 95% CI: 0.9-2.8, p-trend = 0.1). Authors found that calorie intake appeared to be a strong confounder of the relationship between meat (and bioactive meat substances) and gastric cancer. They also recognized the possible recall and misclassification biases that may have been introduced with the use of an FFQ.

61. A case-control study of stomach cancer was conducted in a high risk area of Italy (Palli, Russo, & Decarli, 2001). Between 1985 and 1987, 382 histologically confirmed cases of gastric cancer and 561controls completed a questionnaire on demographic, anthropometric, socioeconomic, residential, occupational, smoking, medical, family, and dietary information in an FFQ of diet patterns in the previous 12 months. NDMA values were estimated by matching the FFQs to Italian food composition tables and ranged from a mean of 0.12 µg/day in the lowest tertile of intake to a mean of 0.33 µg/day in the highest tertile. Dietary intake of NDMA was associated with a non-statistically significant increased risk of gastric cancer (T3 OR = 1.1, 95% CI: 0.8-1.5, p-trend=0.7) after adjusting for various potential confounders. A separate analysis of only the cases did not show a statistically significant increased risk with NDMA intake T3 HR = 1.06, 95% CI: 0.80-1.40, p-trend = 0.6) (Palli et al., 2000). However, a positive family history for gastric cancer strengthened the risk of gastric cancer with NDMA intake (HR = 1.99, 95 % CI: 1.00-3.98).

62. A meta-analysis of dietary nitrate, nitrite and nitrosamine intake and the risk of stomach cancer included 11 cohorts in eight studies published through August 2015, all of which are described above (Song, Wu, & Guan, 2015). All included studies assessed dietary NDMA intake through a questionnaire, then matching the responses to food composition tables. The pooled RR for high vs. low intake of NMDA was 1.34 (95% CI: 1.02-1.76), with significant heterogeneity among the included studies (I^2 = 75.8%, p<0.001). The pooled risk estimate from case-control studies (pooled RR = 2.05, 95% CI: 1.14-3.67) was much stronger than that of cohort studies (pooled RR = 1.09, 95% CI: 0.89-1.33). Sub-analyses by cancer type, publication year, sample size and quality did not result in any significant associations. Ten cohorts were European, whose pooled risk estimate was not statistically significantly increased (pooled RR = 1.18, 95% CI: 0.97-1.43). The remaining study was conducted in Uruguay (De Stefani et al., 1998), which had a very high risk estimate (RR = 3.62, 95% CI:2.38-5.51). Unfortunately, the meta-analysis authors did not also include the follow-up case-control study by the same authors, which is described above (De Stefani et al., 2001). A different group of stomach cancers in Uruguay were examined with an improved FFQ to better estimate dietary intake and control for potential confounding by total calorie intake that was not possible in the previous analysis. The updated study reported a non-statistically significant OR of 1.5 (95% CI: 0.9-2.8) with the highest intake of NDMA. The results of this meta-analysis are limited by several factors. The meta-analysis found statistically significant heterogeneity among the included studies, meaning that there

was statistically significant variation in the effect measure between studies. There is enough variation between studies that indicate further analyses are warranted to explain the study-to-study differences. Authors noted that this heterogeneity for NDMA could not be eliminated completely, even through stratification analyses. A statistically significant pooled risk was observed for case-control studies, but not cohort studies. Case-control studies can be influenced by recall bias because information regarding diet is gathered from the past, and subjects with disease may recall past exposures differently than those without disease. Cohort studies generally have more reliable exposure data because they do not rely on recall of past information, and exposure data is gathered prior to disease development., Even with this strength of cohort study exposure estimation, the NDMA intake was based on self-reported dietary intake in all included studies, which further introduces recall bias into the individual study results.

Upper Aerodigestive Cancers (Larynx, Esophagus, Oral Cavity)

63. Rogers (1995) conducted a study of nitrate, nitrite and NDMA consumption in upper aerodigestive tract cancers in Seattle, Washington (Rogers, Vaughan, Davis, & Thomas, 1995). Newly diagnosed cancers of the larynx, esophagus or oral cavity were identified between September 1983 through February 1987 that had no prior history of cancer or AIDS. Cases were matched on age and gender to population-based controls identified through random-digit dialing of residents in the same three-county area as the cases. A total of 645 cases and 458 controls were included in analyses. All completed a FFQ of usual eating habits over the previous 10 years, with specific attention to NDMA-containing foods. Interviews were conducted to collect information on tobacco and alcohol use, occupation, medical history, dentition, and demographic data. Risk of the three cancers was examined by tertile of daily NDMA intake (<0.06 µg, 0.06-0.179 µg, >0.179 µg). After adjustment for potential confounders, NMDA was not associated at any level of intake with a statistically significant increased risk of either larynx (T3 OR = 1.70, 95% CI: 0.91-3.18, p-trend = 0.23) or esophageal cancer (T3 OR = 1.86, 95% CI: 0.87-3.95, p-trend = 0.06). Cancer of the oral cavity was increased with NDMA intake but was only statistically significant at the highest intake levels (T2 OR = 1.51, 95% CI: 0.92-2.48; T3 OR = 1.82, 95% CI: 1.10-3.00). A dose-response trend was not evident (p-trend = 0.12). Odds ratios were also calculated for cancer risk with specific foods. High intake of smoked fish (1+ times per week), which has a high NDMA content, had a 3-fold increased risk of aerodigestive tract cancer (OR = 3.03, 95% CI: 1.04-8.87), but this was based on a small number of cases (N=13 cases, 7 controls). High intake of beer was associated with an increased risk of oral cavity cancer (OR = 1.79, 1.11-2.88) and esophageal cancer (OR = 2.48, 95% CI: 1.32-4.66), but was not statistically significantly increased for laryngeal cancer (OR = 1.52, 95% CI: 0.83-2.79). Ascorbic acid tended to modify the effect of NDMA intake on both esophageal and oral cavity cancer risk. Compared to high ascorbic acid/low NMDA intake as a reference, high intake of NDMA and low ascorbic acid increased the risk of esophageal cancer 3-fold (OR = 2.96, $p<0.05$) and increased oral cavity cancer risk 2-fold (OR = 2.05, $p<0.05$).

64. A study of meat consumption and risk of esophageal squamous cell carcinoma (ESCC) was conducted in Uruguay between 1996-2004 (De Stefani et al., 2012). Two hundred thirty-four cases of esophageal squamous cell cancer were identified in four major hospitals in Montevideo, Uruguay, as well as 2,020 unmatched controls from the same hospitals with illnesses not related to smoking or alcohol use. Cases and controls were significantly different for gender, current smokers, alcohol drinking, and maté drinking. All participants were administered a questionnaire to collect information on demographics, occupation history, anthropometrics, smoking and alcohol history, intake of nonalcoholic beverages, menstrual history, and an FFQ. Intake of NMDA was one of three meat mutagens that were estimated, but details of the estimation process were not presented. NDMA was found to be associated with ESCC (OR = 3.28, 95% CI: 2.12-5.07, p-trend <0.0001), after adjusting for age, gender, residence, education, BMI, smoking, alcohol use, maté drinking, total energy intake, total vegetables, fruits grains, non-meat fatty foods, and different types of meats.

Colorectal Cancer

65. In 2014, Zhu at al. reported on a study of dietary n-nitroso compounds and colorectal cancer in Canada (Zhu et al., 2014). A total of 1,760 cases that had been diagnosed between 1997-2006 and were between 20-74 years old were identified through regional cancer registries. Population-based cancer-free controls (n=2,481) were frequency matched to the cases on gender and 5-year age categories. All subjects completed a questionnaire on personal and family history and an FFQ of dietary patterns in the previous year. NDMA values were then estimated by assigning values from the National Cancer Institute of Canada nutrient data bank to the FFQ responses and ranged from a median of 0.03 µg/day in quintile 1 to 2.29 µg/day in the highest quintile. Participants were excluded if they had a history of familial adenomatous polyposis, insufficient information on diet or other risk factors, or those with extreme energy intake scores. Cases and controls differed in age, BMI, physical activity, level of education, income, colon screening, NSAID use, hormone replacement therapy, and total energy intake. Intake of NDMA was found to be associated with risk of colorectal cancer at the highest level of intake (Q5 median 2.29 µg/day) (Q5 OR = 1.42, 95% CI: 1.03-1.96), Increased risks were reported for the lower quintiles of exposure, but none were statistically significant. However, a dose-response trend was observed (p-trend = 0.005). When stratified by cancer subsite, trends were observed for increasing risk with increasing NDMA intake for cancer in the proximal colon (p-trend = 0.003) and the rectum (p-trend = 0.01), but not for tumors of the distal colon (p-trend = 0.20). However, only the highest level of intake for cancer of the rectum had a statistically significant increased risk (OR = 1.61, 95% CI: 1.11-2.35). There was no effect modification seen for vitamin C on the risk of colorectal cancer with NDMA intake, but a statistically significant increased risk was seen with high NDMA and low vitamin E intake, (p-interaction = 0.0017). High protein and high NDMA intake also increased risk (OR = 2.16, 95% CI: 1.12-4.15) compared to those with low protein and low NDMA intake, but the interaction was not statistically significant (p-interaction =

0.46). A strength of this study is in the large sample size, but the results are limited by recall and selection biases from the use of self-reported dietary information.

Pancreas Cancer

66. A single study of the risk of pancreas cancer with nitrosamine intake was identified in the literature search, and the only study to report on NDEA intake. A large case-control study of 957 histologically confirmed pancreas cancer cases diagnosed between January 2002 and June 2009 in Texas was published in 2019 (Zheng et al., 2019). Cancer-free controls (n=938) were frequency-matched to the cases by age group, race, and gender. All subjects were interviewed to collection information on demographics, smoking history, family history of cancer, and medical history. No proxy interviews were conducted. 1729 subjects also completed a FFQ from Harvard of dietary patterns in the previous year, and 391 subjects completed an updated version of the FFQ. The update added additional food items, including soy milk and extreme lean hamburger, as well as included open-ended questions for other foods not included. An n-nitroso database was used to assign values to the responses in the FFQs. The cases and controls were similar in age, race and gender as expected with matching, but differed on education level, history of diabetes, smoking status, BMI, family history of pancreatic cancer and alcohol use. Intake of NDMA ranged from 0.09 – 3.45 µg/1000 kcal/day, and NDEA intake was in the range of 0.008 – 0.39 µg/1000 kcal/day. After adjusting for confounders, Intake of NDMA from all food sources was not associated with a statistically significant increased risk of pancreas cancer (Q4 OR = 1.03, 95% CI: 0.78-1.37, p-trend = 0.78). Plant sources of NDMA were associated with a statistically significant increased risk at high levels of intake compared to the lowest level (Q4 OR = 1.93, 95% CI: 1.42-2.61, p-trend <0.0001), but animal sources of NDMA had no statistically significant increased risk (Q4 OR = 1.17, 95% CI: 0.89-1.54, p-trend = 0.26). Increasing intake of NDEA, however, increased the risk of pancreas cancer at all quartiles of intake compared to the lowest level, with ORs for Q2, 3, and 4 reported as 1.35, 1.89, and 2.28, respectively (p-trend <0.0001). No statistically significant increased risks were seen with intake of specific foods, including processed meats that have a high NDMA content.

<u>Confounding factors</u> must be evaluated when assessing causality between an exposure and a health outcome.

67. Confounders are variables that affect both exposure and outcome and can result in a misleading association when not accounted for within the study. There are several potential confounders that should be considered as possible alternative causes for cancers I have considered in this report. It is necessary to consider confounders such as the ones noted below before one can attribute a disease to a specific chemical(s) exposure since confounders can distort the true association observed between an exposure and outcome.

68. <u>Bladder cancer</u>: Various risk factors for bladder cancer have been identified, including the following: smoking, certain workplace exposures (i.e. aromatic amines, dyes),

certain occupations/industries (i.e. paint, rubber, aluminum production, auramine production, magenta production), pioglitazone diabetes medication, herbal supplements containing aristochoic acid, arsenic in drinking water, personal or family history of bladder cancer, other genetic factors, schistosomiasis infection, chemotherapy or radiation therapy to the pelvis. Caucasians are twice as likely to develop bladder cancer as African Americans and Hispanics, and men have a higher risk than women. The risk of bladder cancer increases with age (American Cancer Society, 2019c; Kogevinas, 2018).

69. Blood Cancer: There are three primary types of cancers that arise in the blood, including leukemia, lymphoma, and myeloma, each having several subtypes. Common risk factors for many of these cancers include the following: family history, certain genetic syndromes and exposure to radiation or certain chemotherapy treatments. The risk of some blood cancers is increased with certain viral infections (HIV, Epstein-Barr, HTLV-1) or having a weakened immune system from taking immune-suppression medication. Exposure to benzene increases the risk of leukemia. Most blood cancers occur more frequently in older age groups, and occur more often in men than women, and Caucasians than other ethnic groups. Unlike most blood cancers, smoking is associated only with acute myeloid leukemia (AML). Obesity and African-American race are risk factors specific to multiple myeloma, and having breast implants is a risk factor specific to Non-Hodgkin Lymphoma (NHL) (American Cancer society, 2019a, 2019b, 2019f, 2019g, 2019h, 2019l, 2019p, 2020; Hjalgrim, 2018; Roman, 2018; Smedby, 2018).

70. Breast Cancer: Several risk factors have been identified for breast cancer, including alcohol intake, overweight/obesity, personal or family history of breast cancer, genetics, mammographically dense breasts, benign breast disease, diethylstilbesterol exposure, and ionizing radiation exposure. Hormone levels also play an important role in risk. Early menarche, age at first birth after age 30, high estrogen or androgen levels, postmenopausal hormone therapy, and late menopause (> age 54) all increase breast cancer risk. Risk of breast cancer increases with age as well as height (American Cancer Society, 2019d; Tamimi, 2018).

71. Colorectal cancer: Risk factors that have been identified for colorectal cancer include overweight/obesity, physical inactivity, dietary factors, smoking, alcohol use (in men), age, personal history of colorectal polyps, colorectal cancer, or inflammatory bowel disease, family history of colorectal cancer or adenomatous polyps, Lynch syndrome, familial adenomatous polyposis, and other rare syndromes. Older age, male gender, and being tall also increase colorectal cancer risk. In the U.S., African Americans have the highest incidence and mortality rates of colorectal cancer of all racial groups. Those with Ashkenazi Jewish heritage have the highest rates of colorectal cancer of any ethnic group in the world (American Cancer Society, 2019i; Keum, 2018).

72. Esophageal Cancer: There are two types of esophageal cancer – squamous cell carcinoma and adenocarcinoma. The risk factors differ for each type. The risk factors

that have been identified for squamous cell type include smoking, alcohol, achalasia, inheritable diseases (tylosis, Plummer-Vinson syndrome), esophageal injury, personal history of certain other cancers (lung, oral, throat). Risk factors for esophageal adenocarcinoma include smoking, GERD, Barrett's esophagus, obesity, physical inactivity, and dietary factors (Abnet, 2018; American Cancer Society, 2019k).

73. Gastric Cancer: Identified risk factors for gastric cancer include: *H. pylori* infection, tobacco smoking, ionizing radiation, family history of gastric cancer, some inherited cancer syndromes, MALT lymphoma, dietary factors, anemia, type A blood and previous stomach surgery. Occupations such as foundry, steel, and coal mining, as well as the rubber industry have been associated with increased risks of stomach cancer, but individual compounds have not been implicated. Risk of stomach cancer increases with age, and is more common in men than women, and lower in Caucasians than other races in the U.S. (American Cancer Society, 2019t; Ye, 2018).

74. Kidney Cancer: Risk factors that have been identified for kidney cancer include acquired cystic kidney disease, smoking, obesity, family history of kidney cancer, inherited susceptibility, and hypertension. Kidney cancer is twice as common in men as women, and slightly more common in African Americans than Caucasians (American Cancer Society, 2019m; Zhang, 2018).

75. Liver Cancer: There are several factors that increase the risk of liver cancer, including Hepatitis B or C infection, infection with liver flukes, cirrhosis, certain inherited metabolic diseases, heavy alcohol use, smoking, obesity, type 2 diabetes, certain rare disease, long term exposure to dietary aflatoxins, exposure to vinyl chloride, trichloroethylene, arsenic, Thorotrast, or anabolic steroids (American Cancer Society, 2019n; Bamia, 2018).

76. Lung Cancer: Several risk factors for lung cancer have been well-confirmed, including tobacco smoke, secondhand smoke, genetic susceptibility, exposure to radon or ionizing radiation. Other probable risk factors include personal or family history of lung cancer, exposure to many substances, including asbestos, polycyclic aromatic hydrocarbons, radioactive ores (uranium), arsenic, beryllium, cadmium, silica, vinyl chloride, nickel compounds, chromium compounds, coal products, mustard gas, and chloromethyl ethers, diesel exhaust (American Cancer Society, 2019o; Malhotra, 2018).

77. Pancreatic Cancer: Various risk factors for pancreatic cancer have been identified, including history of chronic pancreatitis, hereditary pancreatitis, family history of pancreatic cancer in a first-degree relative, other cancer syndromes, tobacco smoking, obesity, diabetes. Risk of pancreatic cancer increases with age. Men and African-Americans are more likely to develop the disease (American Cancer Society, 2019r; Benetou, 2018).

78. Pharyngeal Cancer: Well-confirmed risk factors for nasopharyngeal cancer include infection with Epstein-Barr virus, intake of salt-preserved fish, family history of

nasopharyngeal cancer in a first-degree relative, tobacco smoking, and the presence of certain *HLA-A* and *HLA-B* alleles. Occupational exposures to formaldehyde and wood dust have been implicated as risk factors. Nasopharyngeal occurs twice as frequently in men than women. Race/ethnicity is an important factor – those of Asian or Pacific Islander heritage and American Indian/Alaskan Natives have a higher risk than other ethnic groups in the U.S. (American Cancer Society, 2019q; Chang, 2018).

79. Prostate Cancer: Risk factors for prostate cancer include family history of prostate cancer, being taller, mutations of the BRCA1/BRCA2 genes, and Lynch Syndrome. Most prostate cancer cases occur in men over age 65. African-American men develop this disease more frequently than other ethnic groups in the U.S. (American Cancer Society, 2019s; Wilson, 2018)

80. Uterine Cancer: Two common types of gynecological cancer arise from the uterus – cervical and endometrial cancer, each with different risk factors. For cervical cancer, risk factors include specific types of Human Papilloma Virus (HPV), HIV infection, multiple sex partners, sexually active at a young age, diethylstilbesterol exposure, tobacco smoking, long-term oral contraceptive use, multiple births, first birth at less than 20 years (American Cancer Society, 2019e) (Sundstrom, 2018). Risk factors for endometrial cancer include family history in a first-degree relative, high BMI (especially post-menopausal), diabetes, and estrogen exposure factors (high endogenous estrogen levels, post-menopausal estrogen use, nulliparity, infertility, tamoxifen use, polycystic ovarian syndrome, high number of menstrual cycles) (American Cancer Society, 2019j; Crous-Bou, 2018)

81. It is important to consider confounders such as these when conducting a critical evaluation of epidemiological literature related to the chemicals of concern to determine the quality and strength of the studies being evaluated. I note that very few of the risk factors discussed here for each of the cancers of interest were even considered in the epidemiological studies that I reviewed in this case.

Conclusions: NDMA and NDEA intake through diet are not consistently associated with cancer in the medical literature.

82. Overall, positive findings of increased cancer risk associated with NDMA consumption have been noted to be largely from case-control studies which are more susceptible to bias. In contrast, results from large prospective cohort studies are clearly mixed and do not report consistent findings. Some reported significantly increased cancer risk, whereas others reported that cancer risk was either not elevated nor significantly elevated. The study investigators frequently noted potential for measurement error and inability to capture other types of NDMA or NDEA exposures (e.g., endogenous formation) and other chemicals present in the food products as limitations of the studies. Risk of cancer with NDEA exposure was examined in only one study.

83. Additionally, confounding factors (e.g., NDMA exposure from cigarettes, drinking water, household products, endogenous formation, or other chemicals in food) and

biases likely impacted the results, clouding the determination of a true association between dietary NDMA intake and cancer risk.

84. In my opinion, the current scientific evidence (Figure 3) does not support an association between NDMA or NDEA dietary intake and the risk of cancer.

There are <u>many sources</u> of NDMA and NDEA exposure other than valsartan.

Sources of Exposure — NDMA

85. NDMA is an organic chemical that is produced by both industrial and natural processes. Based on physical and chemical properties, NDMA appears to be moderately to very mobile in the environment. NDMA is not currently produced in pure form or commercially used, except for research purposes. It was used previously in liquid rocket fuel production, as an antioxidant, a rubber accelerator, and as an additive for lubricants. NDMA can be unintentionally formed during manufacturing processes involving nitrate or nitrite and alkylamines such as tanneries, pesticide manufacturing, rubber, and tire manufacturing, alkylamine manufacture/use industries, fish processing industries, foundries, and dye manufacturing. NDMA may also be found in the outdoor air, surface water, and soil. However, it does not persist in the environment; it breaks down rapidly in the presence of sunlight (ATSDR, 1989; EPA, 2014). Humans are primarily exposed to NDMA from tobacco smoke, chewing tobacco, diet, especially cured meats such as bacon, beer, fish cheese and other food items, toiletry and cosmetic products (shampoos and cleaners), interior air of cars, and various other household good such as detergents and pesticides (ATSDR, 1989).

86. <u>Exogenous Sources (Diet):</u> In foods, NDMA is formed when secondary amines are exposed to nitrites during processing or preservation (Fristachi and Rice, 2007). Dietary sources of NDMA include beer, fish and fish products, dairy products such as cheese, powdered infant formula, and dried milk products, meat and cured meats, cereals, and vegetables (Fristachi and Rice, 2007). In the 1970s through 1990s, several investigators in various countries measured NDMA content in food products. These results were compiled by the Agency for Toxic Substances and Disease Registry (ATSDR), IARC, and National Toxicology Program (NTP) (ATSDR, 1989; IARC, 1978; NTP, 2016). NDMA levels were reported to be highest in spices used for curing (up to 850 μg/kg) and processed meat and fish products (up to 84 μg/kg). NDMA levels were also relatively high in cheese (up to 68 μg/kg) as compared to other food products. It should be noted that NDMA levels in food products have decreased over the years with regulations on production and processing. In France in the 1970s, beer was estimated to contain 4.4 μg/kg, but decreased to 0.28 μg/kg by the 1990s (Pobel et al., 1995). Herrmann et al. (2014) evaluated processed meat products in Denmark and Belgium and reported that NDMA levels in meat products from Denmark ranged from non-detectable to 4 μg/kg. In 2015, Herrmann et al. indicated that typical intake of NDMA from food and beverages reported in the literature for the German, Finish, and Swedish

populations was ≤1 μg/day (Herrman et al. 2015). For the U.S., Fristachi and Rice (2007) indicated that NDMA intake (all exogenous sources) for adults was 0.11 μg/day.

87. Exogenous Sources (Water): NDMA intake from drinking water was estimated to be a minor source of exogenous NDMA intake compared to other sources, such as food, accounting for less than 10% of lifetime average daily NDMA intake. If endogenous formation is also considered, the contribution of drinking water drops to less than 0.02% (Fristachi & Rice, 2007; Hrudey, Bull, Cotruvo, Paoli, & Wilson, 2013; Richardson, Plewa, Wagner, Schoeny, & Demarini, 2007). NDMA is the most common nitrosamine to be detected in drinking water, usually at levels less than 10 ng/L. In 10% of treated water samples and 27% of chloraminated water samples, concentrations can reach above the minimum reporting level of 2 ng/L (Hrudey et al., 2013). No federal drinking water standards have been established in the U.S. for NDMA (EPA, 2017). California Department of Public Health set a cancer risk level of 3 ng/L/day for NDMA in drinking water within the state, pursuant to California's Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65") California's Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65") (NDMA and Other Nitrosamines - Drinking Water Issues | California State Water Resources Control Board).

88. Alcohol: NDMA has been detected in several different alcoholic beverages, including apple brandy, cider, cognac, Armagnac, rum, and whiskey, at average concentration of 0.1 – 0.4 μg/kg, with a maximum of 1.6 μg/kg. In beer, the average concentration of NDMA was 2 μg/kg, with a maximum of 7 μg/kg (IARC, 1978). In France, the concentration of NDMA in beer was found to be 4.4 μg/kg in the 1970s, which decreased to 0.28 μg/kg by the 1990s due to changes in processing (Pobel et al., 1995).

89. Endogenous Sources (GI formation): NDMA can form endogenously in the gastrointestinal (GI) tract from nitrosation of secondary amines such as DMA, contained in meat and fish and some drugs. Stomach acid reacts with nitrite and nitrate to form nitroso groups, which can then react with amines in food to form NDMA. This formation of NDMA depends on concentrations of nitrate, nitrite, nitrosatable substances, pH, enhancing or inhibitory agents, and the presence of nitrosating bacteria. Many factors can influence nitrosating reactions, making endogenous formation estimates difficult (Fristachi & Rice, 2007). A crude estimate of 45-75% of total exposure to n-nitroso compounds is from endogenous formation from the reaction of nitrite with degradation products of amino acids in the stomach. This estimate was determined from an average total exogenous exposure to n-nitrosamines of 1.10 μmol/day and fecal excretion of 1.56-3.17 μmol/day, and urinary excretion of 1.30 μmol/day (Tricker, 1997).

90. Tobacco: NDMA has been measured in mainstream cigarette smoke at concentrations of 5.7 to 65 ng per cigarette, and in sidestream smoke at 680-1,770 ng. NDMA was found at concentrations of 90 – 240 ng/m^3 in smoke-filled room such as bars, but less than 5 ng/m^3 in residences (IARC, 1978; NTP (National Toxicology Program), 2016).

91. Pharmaceuticals: NDMA and other N-nitrosamines have been found in various drugs. The presence of NDMA was first identified in the ARB valsartan. Following this, several drug product manufacturers voluntarily recalled other products for potential nitrosamine impurities, including some lots of losartan and irbesartan, metformin, nizatidine, and ranitidine (Information about Nitrosamine Impurities in Medications | FDA). NDMA doses varied between products and manufacturers (White, 2020). In September 2020, the Office of Pharmaceutical Quality (OPQ) in the Center of Drug Evaluation and Research (CDER) at the FDA prepared a guidance entitled "Control of Nitrosamine Impurities in Human Drugs: Guidance for Industry, https://www.fda.gov/media/141720/download ," that recommends steps manufacturers of APIs and drug products should take to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products. The US FDA has further set an acceptable level of NDMA in each finished drug product at no more than 0.096µg. Several reasons for the presence of nitrosamine in pharmaceutical products have been explored including the drug's manufacturing process, chemical structure, storage conditions, and packaging (White, 2021).

92. Occupational exposure: Prior to April 1976, NDMA was used in the U.S. in the production of storable liquid rocket fuel which is believed to have contained up to 0.1% NDMA as an impurity. No evidence was found that NDMA is used at present, except for research purposes. Regulations in the US concerning NDMA designate strict procedures to avoid worker contact. Mixtures containing 1.0% or more NDMA must be maintained in isolated or closed systems, employees mut observe special personal hygiene rules, and certain procedures mut be followed for movement of the material and in case of accidental spills and emergencies (NTP (National Toxicology Program), 2016). NDMA can be formed as an unintended by-product of manufacturing processes that use nitrate or nitrite and amines, including tanneries, fish processing plants, foundries, and pesticide, dye, rubber or tire manufacturing plants, and soap/detergent/surfactant manufacturing (ATSDR, 1989; EPA, 2014)(Safety and Health Information Bulletins | N-Nitroso Compounds in Industry | Occupational Safety and Health Administration (osha.gov))

Sources of Exposure — NDEA

93. NDEA is an organic chemical that is produced in small quantities for research purposes. Based on physical and chemical properties, NDEA appears to be moderately to very mobile in the environment. It is widespread in the environment, but rapidly decomposes in sunlight and does not persist in ambient air or water exposed to the sun. NDEA is not commercially produced, but it was formerly used as an additive to gasoline and lubricants, as an antioxidant, as a stabilizer in plastics, fiber industry solvent, copolymer softener, in the synthesis of 1,1-diethylhydrazine and used to increase dielectric constants in condensers (EPA, 2014; NTP (National Toxicology Program), 2016). Humans are exposed to NDEA from diet, especially cured meats and fish, cheese and other food items, alcohol, tobacco smoke and some pharmaceuticals.

94. Exogenous Sources (Diet, Water): Dietary sources of NDEA include fish and fish products, cereals, cheese, meat and cured meats. NDEA levels were reported in concentrations of up to 147 µg/kg in fish, up to 20 mg/kg in salted varieties of fish, over 100 µg/kg in pickled fish, up to 30 µg/kg in cheese, up to 40 µg/kg in cured meats (IARC, 1978; NTP (National Toxicology Program), 2016). In a study of dietary nitroso compounds and pancreatic cancer in the U.S., dietary NDEA intake was found to be 0.008-0.39 µg per 1000 kcal/day (Zheng et al., 2019). California Department of Public Health set a cancer risk level of 1 ng/L for NDMA in drinking water, pursuant to California's Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65") (NDMA and Other Nitrosamines - Drinking Water Issues | California State Water Resources Control Board).

95. Alcohol: NDEA has been detected in several different alcoholic beverages, including apple brandy, ciders, cognac, Armagnac, rum and whiskey, with an average concentration of 0.1 µg/kg (IARC, 1978; NTP (National Toxicology Program), 2016).

96. Endogenous sources (GI formation): A crude estimate of 45-75% of total exposure to n-nitroso compounds is from endogenous formation from the reaction of nitrite with degradation products of amino acids in the stomach. This estimate was determined from an average total exogenous exposure to n-nitrosamines of 1.10 µmol/day and fecal excretion of 1.56-3.17 µmol/day, and urinary excretion of 1.30 µmol/day (Tricker, 1997).

97. Tobacco smoke - NDEA has been measured in tobacco smoke in the range from non-detectable (ND) to 25 ng (Hecht, 2006; IARC, 2004). Up to 8.3 ng per cigarette was found in mainstream smoke, and 8-73 ng in sidestream smoke. Concentrations of up to 0.2 ng/L of NDEA have been found in indoor air polluted with tobacco smoke (NTP (National Toxicology Program), 2016).

98. Pharmaceuticals: Like NDMA, other N-nitrosamines such as NDEA have been found in various drugs. After identifying the presence of nitrosamines in the ARB valsartan, several drug product manufacturers voluntarily recalled other products for potential nitrosamine impurities, including some lots of losartan and irbesartan ARBs, metformin, nizatidine, and ranitidine (Information about Nitrosamine Impurities in Medications | FDA). Nitrosamine doses varied between products and manufacturers (White, 2020). In September 2020, the FDA recommended steps manufacturers of APIs and drug products should take to detect and prevent unacceptable levels of nitrosamine impurities in pharmaceutical products (https://www.fda.gov/media/141720/download). The US FDA has further set an acceptable level of NDEA in each finished drug product at no more than 0.0265µg. Several reasons for the presence of nitrosamines in pharmaceutical products have been explored including the drug's manufacturing process, chemical structure, storage conditions, and packaging (White, 2021).

99. Occupation: NDEA is not commercially produced currently, but it was formerly used as an additive to gasoline and lubricants, as an antioxidant, and as a stabilizer in plastics

(NTP (National Toxicology Program), 2016). NDEA can be formed as an unintended by-product of manufacturing processes in the rubber, dye, and metal foundry industries (PubChem, 2021a).

The Bradford-Hill Criteria are used to assess causality in the medical literature. As discussed below, the body of evidence on NDMA and NDEA and cancer fail to demonstrate causality.

100. The Bradford-Hill criteria are used to examine the totality of the evidence. Using one or two studies for each criterion is not an acceptable method to use the criteria. One must evaluate all the evidence together in context of the criteria.

101. Strength of Association

a. This guideline refers to the magnitude of the effect of an exposure on a disease. Strong associations are less likely to be explained by confounding or bias than weak associations. It should be emphasized that one does not even reach the point of examining the strength of a reported association unless the study in question is free of significant bias and confounding. That is, that bias, chance, and confounding can be ruled out as plausible explanations for the association observed in the study.

b. The studies that examined the risk of cancer with NDMA exposure had mixed results**.** In studies of NDMA exposure from prescription medications including valsartan, two studies of cancer related to these medications using reports of adverse events to the U.S. FDA observed increased reporting of cancer, but this data had serious limitations. The FDA stated that this data cannot be used as evidence that a medication is associated with an adverse outcome due to the information being self-reported and unverified. Two other studies of potentially NDMA-containing medication analyzed health insurance data and found no evidence of increased cancer with use of these medications. Strong associations between exposure to NDMA from medication and risk of cancer have not been observed**.** No studies were identified that examined risk of cancer with NDEA from medication.

c. In studies of dietary intake of NDMA or NDEA, findings of increased cancer risk associated with NDMA consumption were inconsistent. Risks for most specific cancer sites were reported in three or less studies each, with the exception of stomach and esophageal cancers. For stomach cancer, increased risks were largely from case-control studies which are more prone to bias. In contrast, results from large prospective cohort studies were mixed and did not report consistent findings. Some reported significantly increased cancer risk, whereas others reported that cancer risk was either not elevated or not significantly elevated. Of four studies reporting risk of esophageal cancer, three reported no

statistically significant increased risk. Investigators of dietary NDMA studies frequently noted potential for measurement error and inability to capture other types of nitrosamine exposures (e.g., endogenous formation) and other chemicals present in the food products as limitations of the studies.

d. Risk of cancer with NDEA exposure was examined in only one study.

e. Strong, consistent associations between exposure to NDMA or NDEA intake and cancer were not observed in the studies that were reviewed to fulfill this criterion for causation.

102. Dose-Response

a. This consideration focuses on whether the study data exhibit a dose-response relationship between the exposure of interest and the disease, such that an increase in exposure is associated with an increase in the incidence of the disease, and vice versa.

b. No dose-response relationship was seen between increasing risk of cancer with increasing exposure to potentially NDMA-containing medication in the two studies that reported risk of cancer with increasing levels of NDMA exposure from medication use (Pottegard 2018, Yoon 2021). The two studies that examined adverse event reports to the FDA did not have the ability to examine dose-response associations in the data.

c. None of the diet studies measured intake of NDMA or NDEA quantitatively. Rather, FFQs and other diet questionnaires were used to estimate exposures based on usual diet patterns in the previous 12 months in most cases. FFQs and other diet surveys measure intake using a qualitative or semi-quantitative scale. These are indirect measures of exposure and are considered appropriate for ranked analyses only. FFQs are self-reported dietary patterns that people tend to report in a way that makes them look best, which may misclassify their actual exposures. These tools may not be able to capture a subject's complete diet if certain foods in an individual's diet are not included. For example, in the 1998 case-control study of stomach cancer in Uruguay, an increased risk was observed with NDMA intake with a dose-response trend ($p<0.001$) measured both categorically and continuously (DeStefani 1998). However, the authors noted that they used a short FFQ that did not allow for adjustments by total calorie intake. The authors then conducted a second study of stomach cancer using a more robust FFQ in the same region (DeStefani 2001). Adding the adjustment for total calorie intake, no association between increasing NDMA and increasing stomach cancer risk was observed (p-trend =0.1).

d. Increasing risk of cancer with increasing dietary intake of NDMA and NDEA was seen sporadically. Statistically significant increased risk of several cancers was observed with increasing dietary NDMA intake, but not consistently for any specific cancer site. Dose-response trends were generally reported by case-control studies, and not cohort studies. Recall bias is an important limitation with the use of FFQs, especially in case-control studies, where subjects with and without disease are identified prior to asking about exposures. Subjects with cancer may recall past exposures differently than those without disease. Cohort studies measure exposure more accurately than case-control studies because they are measured in present time rather than recalling past exposures, and they are measured prior to disease development. These studies found a few sporadic dose-response relationships between NDMA and different cancers, but these patterns were not consistent between the studies.

e. NDEA intake was only reported in one case-control study of pancreas cancer, in which a strong dose-response trend was found ($p<0.0001$).

f. Evidence of increasing risk of cancer with increasing exposure has not been consistently shown that could not be explained by bias, chance or confounding in support of a causal association between NDMA or NDEA and risk of cancer.

103. Replication

a. Repetition of the same or similar results in a number of different independent studies lessens the likelihood that the association observed in a particular study or studies was due to chance, unsuspected bias, or confounding.

b. In four studies of the use of two different NDMA-containing medications and risk of cancer using health insurance data in several different countries, a small increased risk of liver cancer was observed in one study, but no associations were found in the other three indicating that this criterion was not met.

c. Studies of dietary NDMA were conducted in many different populations around the world, including, Italy, France, Uruguay, United States, and others and examined the risk of many types of cancer, including esophageal, head and neck, colorectal, stomach, bladder, pancreas, and lung cancers. Each of the studies estimated exposures similarly using FFQ tools. Some studies found associations between NDMA intake and cancer, and others did not. The most extensively studied cancer was stomach cancer, which had inconsistent findings with NDMA intake. Several cohort studies (Knekt 1999, Loh 2011) found non-statistically significant decreased risks of stomach cancer with dietary NDMA intake. The cohort study of Dutch cancer cases

found an association between NDMA and non-cardia gastric cancers in men only (Keszei 2013) but not in other types of gastric cancer or in women. Another cohort study (Jakszyn 2006) found increased risks in both men and women, with dose-response trends. Five case-control studies of stomach cancer (LaVecchia 1995, Pobel 1995, DeStefani 1998, DeStefani 2001, Palli 2001) also reported inconsistent risks with dietary NDMA. As described above, exposure data in dietary studies are subject to significant sources of bias that limit their use in the determination of causality.

d. The risk of cancer with NDMA exposure from two different medications showed no associations in three of the four studies that used health insurance or registry data. Among dietary studies, consistent results have not been observed between studies of exposure to NDMA and risk of cancer that could not be explained by bias, chance or confounding. Only one study was conducted on the association of cancer with NDEA intake. Overall, consistent replication of results in different settings and exposure scenarios has not been established for NDMA or NDEA and risk of cancer.

104. Specificity

a. As originally articulated by Sir Austin Bradford Hill, the inquiry is whether (a) the reported association is limited to a specific characteristic (such as work in each occupation) and to particular sites and types of disease, and (b) there is no association between that characteristic or exposure and other causes of death.

b. The cancer outcomes were specified similarly in all studies except the studies of U.S. FAERS data. The FAERS data is reliant upon self-reported, unverified reports of cancer from consumers, medical professionals, and others. In all other studies, ICD codes and/or histologic confirmation of cancer were used to identify cases.

c. Many cancer sites were examined, each of which has different risk factors that must be considered in analyses for an accurate estimation of risk with NDMA or NDEA exposure. Many of these risks were controlled for in models, but most authors recognized that they were not able to include sources of NDMA and NDEA other than diet or specific medications in their analyses. As described above, there are many other sources of NDMA and NDEA exposure, especially endogenous formation in the GI tract. Other risk factors, if not well-controlled for can also influence the results.

d. The U.S. EPA evaluated the carcinogenicity of both NDMA and NDEA and found that human exposure to nitrosamines usually comes from mixtures of substances, such as other nitrosamines or tobacco smoke. Due to potential confounding by these other substances that occur with

exposure to NDMA or NDEA, data from human exposure studies was of limited use in the evaluation of the carcinogenicity of individual nitrosamines (EPA IRIS, 1987a, 1987b). For example, in the reviewed studies included in this report, risk of lung cancer was found to increase with increasing NDMA intake in both case-control studies that examined this risk (De Stefani et al., 1996; Goodman et al., 1992). Both studies controlled for several confounders, including pack-years of smoking. However, De Stefani also stratified the analyses by smoking history and found the increased risk of lung cancer with increasing NDMA intake was only present in current smokers. Non-smokers and ex-smokers had non-statistically significant increased risks at all levels of NDMA intake. Residual confounding by the very strong risk factor of smoking may have influenced the overall risk of lung cancer in both studies.

e. The outcomes examined were specific, but co-exposures from other sources of NDMA or NDEA or other substances prevent establishing the specificity of exposures required by this consideration for causality that could not be explained by bias, chance, or confounding.

105. Biologic Plausibility

a. This guideline relates to whether there are known biological mechanisms in the fields of biology, toxicology, and other fields that explain the hypothesized causal relationship between the exposure and the disease.

b. Both NDMA and NDEA are used to induce tumors in laboratory animals (PubChem, 2021a, 2021b). From the published literature, regulatory agencies have determined that NDMA and NDEA cause cancer in animals, but they did not find consistent evidence of this in humans, which prevented them from classifying these substances as known human carcinogens. Rather, they were considered probable or likely to be human carcinogens.

c. It is biologically plausible that NDMA and NDEA cause cancer, therefore this criterion for causation between NDMA or NDEA and cancer has been fulfilled.

106. Temporality

a. Temporality refers to the fact that causal relationships require that the exposure of interest precede the disease. In all studies examined, the exposures examined preceded the disease. For example, In the study of NDMA exposure from valsartan use in the Danish population, authors used a lag time of one year between starting a valsartan prescription and diagnosis of cancer (Pottegård et al., 2018). Similarly, Korean patients were required to have used ranitidine for one year and be cancer-free to

be included in the study (Yoon et al., 2021). All dietary studies utilized FFQs to estimate NDMA and NDEA intake from food and beverages. Subjects were asked about dietary patterns in the 12 months or more prior to disease development to make these estimations.

b. This criterion of temporality has been fulfilled for evidence of causation between NDMA and NDEA and risk of cancer.

107. Coherence

a. Coherence requires that no serious conflict between a causal interpretation of the association and established knowledge of the natural history and biology of the disease in question exists. The above criteria of strength of association, consistency, and specificity have not been met in the studies that were evaluated. Since a causal interpretation of the relationship between NDMA or NDEA and cancer is not established, this criterion cannot be evaluated.

108. Analogy

a. This Bradford Hill guideline asks whether a persuasive analogy can be drawn between the hypothesized cause-and-effect relationship being evaluated and a known causal relationship involving a similar (type of) environmental agent and similar diseases.

b. NDMA and NDEA are members of the class of nitrosamines. Many members of this group have carcinogenic and mutagenic properties (PubChem, 2021c). In IARC Monograph 17, many members of the nitrosamine class were reviewed for carcinogenicity (IARC, 1978). In 16 of the 17 nitrosamine compounds, sufficient evidence of carcinogenicity was found in animals, but there was not sufficient evidence in humans. The National Toxicology Program's 14th Edition of the Report on Cancer in 2016 evaluated 15 nitrosamine compounds and came to similar conclusions as IARC (NTP (National Toxicology Program), 2016).

c. Other nitrosamines were found to behave similarly to NDMA and NDEA in their carcinogenic properties in animals, but none have been found to have sufficient evidence of carcinogenicity in humans. Therefore, the criterion of analogy has not been fulfilled to establish causation between NDMA or NDEA and cancer.

109. Experimental Evidence

a. This guideline refers to experimental evidence in animals and mechanistic evaluations to support a causal association.

b. Both NDMA and NDEA are used to induce tumors in laboratory animals (PubChem, 2021a, 2021b). The carcinogenicity of NDMA and NDEA

was reviewed by IARC and the U.S. EPA and found evidence that both NDMA and NDEA cause cancer in many species of animals, including mice, rats, hamsters, guinea pigs, rabbits, ducks, mastomys, various fish, newts and frogs. It induces both benign and malignant tumors by both ingestion and inhalation in various organs. Evidence of mutagenic action was also found in cell lines (EPA IRIS, 1987a, 1987b; IARC, 1978).

c. There is experimental evidence in animals and cell lines to support this criterion for NDMA and NDEA, but no experimental evidence in humans.

110. The studies of NMDA and NDEA medication do not meet any of the Bradford-Hill criteria for causality.

111. When reviewing all of the studies of diet and cancer together, the association of foods containing NMDA and NDEA and cancer cannot be considered causal in light of the Bradford-Hill criteria.

Evaluation of epidemiologic research by respected Scientific Bodies confirm that studies do not show a relationship between NDMA and NDEA and cancer.

Regulatory agencies have generally classified NDMA and NDEA as suggestive or probable human carcinogens. No agency has given NDMA or NDEA the highest level of grading for carcinogenicity, due to limited evidence in human studies. The classifications are based mainly on animal evidence.

112. <u>International Agency for Research on Cancer (IARC)</u>

a. NDMA - In the 1978 monograph on n-nitroso compounds published by IARC, there were no epidemiologic studies in human available for review (IARC, 1978). They found that the general population may be exposed to low levels of NDMA, but no exposed group had yet been identified that was suitable for an epidemiologic study. They concluded that there was *sufficient evidence* of a carcinogenic effect of n-nitrosodimethylamine in experimental animal studies. Even though no epidemiological data were available, NDMA should be regarded for practical purposes as if it were carcinogenic to humans. There has not been an update to this monograph.

b. NDEA – In the same 1978 monograph, IARC found no epidemiologic studies in humans on health effects of NDEA exposure (IARC, 1978). It was concluded that there was *sufficient evidence* of a carcinogenic effect of n-nitrosodiethylamine in experimental animal studies. Even though no epidemiological data were available, NDEA should be regarded for practical purposes as if it were carcinogenic to humans.

c. NDMA and NDEA are both classified as Group 2A agents, which does not mean they have a causal relationship to cancer in humans. This category generally applies when the Working Group, the group of scientists assembled by IARC to evaluate the chemical, has made at least two of the following evaluations, including at least one that involves either exposed humans or human cells or tissues:

   i. Limited evidence of carcinogenicity in humans,
   ii. Sufficient evidence of carcinogenicity in experimental animals,
   iii. Strong evidence that the agent exhibits key characteristics of carcinogens.

d. *Limited evidence of carcinogenicity* is defined as a causal interpretation of the positive association observed in the body of evidence on exposure to the agent and cancer is credible, but chance, bias, or confounding could not be ruled out with reasonable confidence.

e. Thus, given the body of evidence that is presented above and its inability to rule out chance, bias, or confounding, NDMA and NDEA are considered to have limited evidence of carcinogenicity in humans by IARC.

113. World Health Organization (WHO)

In 2002, two scientists from Canada, representing the International Program on Chemical Safety, which is a cooperative program of the World Health Organization, the International Labor Organization, evaluated NDMA for a Concise International Chemical Assessment Document (CICAD). No specific classification system has been developed for the CICAD. It must be noted that the document states (Liteplo, 2002. Page 1) that the CICAD is 'not a summary of all available data on a particular chemical'. In fact, when comparing our systematic literature review with the Liteplo, 2002 document for scientific articles published prior to 2002, we find 10 articles as opposed to the 8 articles identified by Liteplo.

Liteplo (2002) reviewed the health effects of NDMA and found that epidemiologic studies in humans were limited, but the results were suggestive of an association between NDMA and several cancers, in particular gastric cancer and lung (Liteplo, 2002). These studies of the effects of NDMA exposure in humans reported associations between gastric cancer in three of four studies (González et al., 1994; La Vecchia et al., 1995; Pobel et al., 1995; Rogers et al., 1995), and lung cancer in two studies (Goodman 1992, DeStefani 1996). It was noted that these studies were limited by the use of dietary recall to estimate exposures and did not control for confounding factors such as alcohol.

A single cohort study of NDMA exposure was found to have an increased risk of colorectal cancer at the highest levels of exposure, but not stomach or head and neck cancer (Knekt 1999). No significant dose-response trend was observed for any cancer ($p > .05$). Also, the

lack of a relation between NDMA and stomach cancer further limited the findings of the four cases-control studies and gastric cancer (González et al., 1994; La Vecchia et al., 1995; Pobel et al., 1995; Rogers et al., 1995).

However, because of evidence in animal studies and the similarity of NDMA metabolism in humans and other species, NDMA was felt to be highly likely by the authors of the CICAD to be carcinogenic to humans. No evaluation of NEDA was conducted.

114. U.S. Environmental Protection Agency (EPA)

Similar to the classifications used by IARC, the U.S. EPA uses three categories of data to evaluate carcinogenicity of an agent: human data, experimental animal studies, and supporting data including genotoxicity, pharmacokinetic and metabolic studies (U. EPA, 2021). Under the 1986 risk assessment guidelines, the weight of evidence is categorized as follows:

- Group A: Carcinogenic to humans. Agents with adequate human data to demonstrate a causal association of the agent with human cancer (typically epidemiologic data).
- Group B: Probably carcinogenic to humans. Agents with sufficient evidence (indicative of a causal relationship) from animal bioassay data, but either limited evidence (indicative of a possible causal relationship, but not exclusive of alternative explanations; Group B1), or with little or no human data (Group B2).
- Group C: Possibly carcinogenic to humans. Agents with limited animal evidence and little or no human data.
- Group D: Not classifiable as to human carcinogenicity. Agents without adequate data either to support or refute human carcinogenicity.
- Group E: Evidence of non-carcinogenicity. Agents that show no evidence for carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

    a. NDMA – The U.S. Environmental Protection Agency's Integrated Risk Information System (EPA IRIS) published a Weight of Evidence for Cancer for NDMA in 1987 (EPA IRIS, 1987b). NDMA was classified as a ***B2, or probable human carcinogen***. This classification was based solely on animal studies, as the EPA felt that human exposure to nitrosamines included mixtures of chemicals containing these chemicals, such as cutting oils and tobacco products. Because of the potential for confounding by these substances, human exposure data was thought to be of limited use in the evaluation of the carcinogenicity of specific nitrosamines.

b. NDEA – NDEA was also classified as a ***B2, or probable human carcinogen*** in 1987, with the same exposure data limitations in human studies as NDMA (EPA IRIS, 1987a).

c. Similar to the classification by IARC, the US EPA considers the body of scientific evidence pertaining to NDMA and NDEA to not cause cancer in humans.

115. National Toxicology Program (NTP)

The NTP uses the following criteria for evaluating carcinogenicity from studies in humans, animals and mechanistic studies in the Report on Carcinogens (RoC) (National Toxicology Program, 2015):

- Known to be a human carcinogen: Sufficient evidence of carcinogenicity from studies in humans.
- Reasonably anticipated to be a human carcinogen:
  - Limited evidence of carcinogenicity from studies in humans, or
  - sufficient evidence of carcinogenicity from studies in experimental animals, or
  - the substance belongs to a structurally related class of substances that are listed in the RoC, or there is convincing relevant information that the agent acts through a mechanism indicating that it would likely cause cancer in humans.

a. NDMA – In their Report on Carcinogens, 14th edition in 2016 (NTP (National Toxicology Program), 2016), found results of most studies of NDMA and cancer risk to be confounded by other exposures and smoking and alcohol use, as well as other nitrosamines in the diet. There were no studies of occupational exposure to NDMA identified. They classified NDMA as ***reasonably anticipated*** **to be a human carcinogen** based on sufficient evidence of carcinogenicity from studies in experimental animals.

b. NDEA — In 2016, the NTP also classified NDEA as ***reasonably anticipated*** **to be a human carcinogen** based on sufficient evidence of carcinogenicity from studies in experimental animals (NTP (National Toxicology Program), 2016). No epidemiological studies were identified that evaluated the relationship between human cancer and exposure specifically to *N*-nitrosodiethylamine.

c. The NTP does not believe there is sufficient evidence in humans to demonstrate that NDMA and NDEA are associated with cancer.

116. Agency for Toxic Substances and Disease Registry (ATSDR)

The ATSDR relies on the cancer classifications of the NTP, IARC and EPA, but discusses the weight of evidence in the Toxicological Profiles of each agent.

a. NDMA – In the 1989 Toxicological Profile of NDMA, no studies of carcinogenic effects of NDMA by inhalation, oral or dermal exposure were identified. It was stated, "Although there are no reports of NDMA causing cancer in humans, it is ***reasonable to expect*** that exposure to NDMA by eating, drinking, or breathing could cause cancer in humans." (ATSDR, 1989).

b. NDEA – There has not been a Toxicological profile of NDEA published.

117. U. S. Food and Drug Administration (FDA)

a. On July 13, 2018, the FDA announced a voluntary recall of several drugs containing valsartan due to impurities with NDMA **(**FDA announces voluntary recall of several medicines containing valsartan following detection of an impurity | FDA). On May 2, 2019, the FDA released its laboratory analysis results for NDMA and NDEA in valsartan products (Laboratory analysis of valsartan products | FDA). Based on lab test results and record from the manufacturers of the recalled valsartan lots, the FDA stated that the impurities may have been present in the valsartan-containing finished drug lots for up to four years. The estimated safety risks to patients were calculated based on the highest daily dose, knowing that many people took lower doses, so the risk would be less than calculated:

b. NDMA estimated risk: FDA estimated that if 8,000 people took the highest valsartan dose (320 mg) containing NDMA from the recalled batches daily for four years, there may be *one additional case of cancer* over the lifetimes of the 8,000 people.

c. NDEA estimated risk: FDA scientists estimated that if 18,000 people took valsartan at the highest dose (320 mg) containing NDEA from recalled batches daily for four years, there may be *one additional case of cancer* over the lifetime of these 18,000 people. NDEA has a marginally lower cancer risk estimate than NDMA because NDEA levels were lower than levels of NDMA in drug samples.

d. On February 29, 2019, the FDA released updated interim acceptable intake limits for NDMA and NDEA impurities to guide manufacturers to conduct a voluntary recall if testing revealed nitrosamines above these levels in their finished products. Acceptable intake was calculated as a daily exposure to NDMA/NDEA that approximates a 1:100,000 cancer risk after 70 years exposure. For a maximum dose of Valsartan of 320 mg/day, these limits were:

i. NDMA: 96 ng/day or 0.3 ppm

ii. NDEA: 26.5 ng/day or 0.083 ppm

Plaintiff expert reports fail to demonstrate a relationship between NDMA or NDEA and cancer in humans.

Dr. Hecht

118. I have reviewed the report by Dr. Hecht and found it did not contain a description of a systematic methodology used to evaluate a body of literature that is necessary to make claims of general causation. Dr. Hecht did not define a literature search strategy, nor a systematic method of evaluating the evidence to determine general causation. Good scientific method involves developing a process to identify studies and evaluate both qualitative and quantitative data. He did not provide keyword search terms or inclusion/exclusion criteria used to get to the final set of literature he reviewed. Evaluation of the totality of the evidence is required to form an opinion on the causality of an exposure and disease.

119. Dr. Hecht selected conclusions from publications that showed an association between NDMA exposure and cancers as evidence of an association without presenting any risk estimates or statistical significance testing. Of the studies of dietary NDMA he cited, Dr. Hecht dismissed studies that did not find an association with a general statement that "To the extent these or other studies do not find a significant association, or raise questions, this can be explained by small or relatively small sample size, inadequate follow up period to capture all cancers, bias/inadequate dose quantification, potentially mitigating dietary factors such as vitamin C intake, and others." No evaluation of the strengths and limitations of the entire body of evidence he reviewed was apparent. The limitations that he points out are potentially true of most studies of dietary intake – bias or inadequate dose quantification due to the use of FFQs, and lack of control for other confounding factors.

120. Dr. Hecht cites the Gomm (2021) report of cancer risk with intake of NDMA-containing valsartan prescriptions as evidence that valsartan containing NDMA increased the risk of cancer. The Gomm (2021) study found a slightly elevated risk for liver cancer only. There were many shortcomings of this study that I described above, including that the investigators did not control for other risk factors for liver cancer, and the short follow-up time for cancers to be able to develop and be detected. Dr. Hecht did not discuss any of these limitations. This study does not provide strong evidence of causation.

121. Overall, Dr. Hecht did not systematically evaluate the evidence, discuss the strength of associations observed in the literature, consistency of findings, bias and confounding or dose-response relationships to be able to properly evaluate the evidence for an opinion on the general causation of NDMA and risk of cancer.

Dr. Lagana

122. Like Dr. Hecht, Dr. Lagana did not provide any methodology for systematically reviewing the body of literature related to NDMA and cancer risk to form opinions regarding general causation. It is unknown how he selected the published evidence to make an informed opinion. He also provides no risk estimates or statistical significance testing as evidence of causation.

123. Dr. Lagana improperly used the Bradford-Hill criteria to establish causation. He stated which criteria a particular study applied to, rather than using Bradford-Hill to collectively determine if the totality of the evidence (all the literature on a specified topic) was sufficient to determine causation. For example, Dr. Lagana discussed the heterogeneity of the literature, citing studies that reported statistically significant associations, those that did not, and inconclusive studies, but somehow concluded that the overall body of epidemiological evidence fulfilled Hill's seventh criteria of epidemiology supporting laboratory data. The heterogenous findings he described do not support causation.

124. Studies of rubber workers that were potentially exposed to NDMA were cited as evidence of an association without any discussion of the number of co-exposures these employees were also exposed to and if they were adequately controlled for. In addition to nitrosamines, workers in the rubber industry are exposed to rubber dust and fumes, polycyclic aromatic hydrocarbons, phthalates, aromatic amines, and solvents including benzene, and others (Hidajat et al., 2019). For example, in the study of British rubber and tire workers by Hidajat (2019), associations were reported between NDMA exposure and multiple cancer outcomes in workers between 1967 and 2015. However, there are several serious limitations that cause any conclusions to be interpreted cautiously. First, the study used measures of airborne NDMA, several other nitrosamines, rubber dust and rubber fumes exposures from a database of measurements taken in European rubber factories. These measures were used to create a job-exposure matrix and estimate average exposures. Because job information was only available for one year (1967), an assumption was made that all subjects remained in the same department but not necessarily the same job throughout their careers. Using a job-exposure matrix to estimate exposures, and the assumption that employees did not move departments introduces misclassification biases if exposures were not similar throughout the departments, or workers moved around the same department frequently, with different exposures in different areas. Air measures of NDMA may not accurately reflect the dose a worker experiences, because a portion of what is inhaled is then exhaled. If the chemical mixtures or processes are different across the European rubber manufacturing industry, the measures used to estimate exposure may not reflect the true experience in the facility where the study subjects worked. Analyses were adjusted for lifetime cumulative exposure to rubber dust, rubber fumes or N-nitrosamines, but workers in the rubber industry are exposed to many different chemicals, there was likely residual confounding from other co-exposures. Authors stated that cross-contamination between departments was possible and could not be modelled in the analyses. There was no adjustment for the

important confounders of smoking or other lifestyle factors that play a significant role in cancer development. Finally, some of the workers had been employed since the 1930's when there were no adequate worker protections. These shortcomings limit the use of this study, and other rubber worker studies, as evidence of causation. It is absurd to suggest that workers in this study had similar levels of exposure to NDMA as valsartan users and that any findings of this study are applicable.

125. Overall, Dr. Lagana did not systematically evaluate the evidence, discuss the strength of associations observed in the literature, consistency of findings, bias and confounding or dose-response relationships to be able to properly evaluate the evidence for an opinion on the general causation of NDMA and risk of cancer.

Dr. Etminan

126. Dr. Etminan conducted a systematic review of the literature and provided his methodology, including search terms to identify studies as well as inclusion and exclusion criteria. However, after stating that his exclusion criteria included studies that did not quantify nitrosamines or NDMA concentrations, he said these studies were not actually excluded, but reviewed and not weighted strongly in his assessment of risk.

127. Dr. Etminan relied on studies of rubber industry workers for evidence of causation, including the study of British rubber workers by Hidajat (2019) (Hidajat et al., 2019), which he graded as a well-conducted study of occupational NDMA exposure. He discussed that the study did not control for smoking or family history of cancer, but did not address the limitations of the exposure estimation performed using a JEM and limited work history information. The serious limitations described above should have prevented Dr. Etminan from using this study as a high level of evidence for causation. Yet Dr. Etminan relied largely on the results of the Hidajat study for strength of evidence and dose-response in his evaluation using Hill criteria. Dr. Etiminan is incorrect that workers in this occupational study had similar levels of exposure to NDMA as valsartan users.

128. Dr. Etminan also used studies of dietary NDMA intake as evidence of causation, after pointing out that these types of studies have biased results, "Although dietary epidemiologic studies might be prone to bias, the totality of the evidence is suggestive that the increase in the risk of cancer with NDMA cannot be explained by bias." As I discussed above, diet studies, and especially case-control diet studies, suffer from many limitations that make the exposure estimates unreliable. Dr. Etminan discusses the imprecision of the use of dietary questionnaires to quantify NDMA exposure from food, but only in the context of the Knekt study (Knekt et al., 1999) that did not find an increased risk of stomach cancer. He did not globally address this imprecision in all diet studies included in his review.

129. Dr. Etminan was incorrect in stating that because studies found few numbers of cancer outcomes in the study populations, they were underpowered. For example, he

stated that the occupational study by Straif (Straif et al., 2000) was underpowered to appropriately examine pancreatic cancer deaths because only 15 pancreatic cancer deaths were identified in a cohort of 8933 rubber workers. No increased risk was found in either workers in the medium or high nitrosamine exposure categories. In contrast, he claimed that the larger study of over 36,000 British rubber workers by Hidajat (2019) was better powered because more pancreas cancer cases were identified, and an increased risk was reported. Later in his report he then says that the large Hidajat study did not find an increased risk of larynx cancer, due to the study only identifying 62 cases of laryngeal cancer. "If Hidajat had been more well-powered to detect laryngeal cancer (i.e., had more laryngeal cancer events) it is likely that the increased risk would have become statistically significant." Power is the probability of observing an effect in the population if one of a specified effect size or greater exists in the population (C. H. Hennekens, Buring, J.F., 1987). Power is set during the design phase of the study and is not dependent on the numbers of outcomes identified. Dr. Etminan has a misunderstanding of power and the ability of a study to detect increased risks within a population or is using a misleading argument to explain away non-statistically significant results.

130. Dr. Etminan also misrepresents the interpretation of confidence intervals around a risk estimate in his discussions of the literature. Specifically, he stated in the section where he reported results from Straif (page 18 of his report) "No risk with rectal cancer deaths (0.80, 95% CI: RR 0.2-3.9) was observed although the wide confidence intervals (due to only 19 deaths due to rectal cancers) including an upper bound of 3.9 does not exclude an increase in risk." Further, he states in a different section of his report when commenting on the Pottegard (2018) study that "the upper bound of the confidence intervals for all the 9 cancers were clinically significant with the lowest being 1.73 and the highest 5.9 (Figure 3, Pottegard 64), which do not exclude the possibly of an increase in risk of the 9 cancers with NDMA". However, the 9 cancers also have lower bound estimates from 0.15-0.85 indicating that there is an equally likely chance that in this study NDMA is protective from these cancers.

131. Results that are not statistically significant should not be used as evidence of a possible association, but he does just that. Because the upper bound of the confidence intervals were above 1.0, Dr. Etminan argued that the results did not exclude the possibility of an increased risk for these cancers. However, since the lower bound estimates where < 1 the results also do not exclude the possibility of a reduced risk for these cancers. A confidence interval represents the range in which the true estimate will be 95% of the time. He described this concept early in his report, and stated that if a confidence interval contains 1.0, these results are not statistically significant and can be interpreted as inconclusive or imprecise.

132. In summary, while Dr. Etminan claims to have conducted a systematic literature review, he did not evaluate all studies equally for their strengths and limitations to

determine if the evidence was indicative of a causal association. Further, he misrepresented the concept of confidence intervals.

Dr. Madigan

133. Like several of the other experts, Dr. Madigan did not describe a systematic methodology for a review of the literature that he conducted which enabled him to form opinions on general causation between NDMA and cancer risk. Rather, he relied on the studies evaluated by Dr. Etminan as the basis of his statistical analysis and calculations of lifetime cumulative exposure (LCE) to NDMA.

134. Dr. Madigan calculated the lifetime cumulative exposure (LCE) for NDMA in each of these dietary NDMA studies as well as a study of occupational NDMA exposure to attempt to determine what level of NDMA exposure is associated with increased cancer risk. In his calculations of LCE from diet studies, he used the NDMA estimates from the top quartile of self-reported NDMA intake from the past 12 months in diet studies. These calculations therefore assume that a subject's diet pattern remained the same throughout their lifetime. These self-reported measures are already biased in cancer cases in case-control studies, because subjects with cancer likely recall diet patterns in the previous year with a different perspective than those without cancer. Also, individuals with a disease such as cancer may have altered their diet in the previous year in ways that the control subjects may not have.

135. Dr. Madigan also used the Hidajat (2019) study of rubber workers to calculate an LCE. Hidajat used NDMA indirect exposure estimates from a job-exposure matrix using a database of exposure measures taken from European rubber manufacturing facilities. Job-exposure matrices are not direct measures of the job exposures, but a best-guess based on similar jobs in other facilities. NDMA air measures may not reflect the true dose experienced by an employee, because a portion of the NDMA inhaled is then exhaled. Beyond that, as described above, the study only had job information for a single year and had to assume employees remained in the same department for their entire career, which may not have been accurate. Coupling the biases within the study of possible exposure misclassification using a JEM and a single year of work history, Dr. Madigan's calculations assumed occupational exposure to NDMA was respiratory and remained constant throughout their career. These calculations also did not consider diet or other sources of NDMA exposure, or co-exposures with other potential carcinogens in the workplace. These LCEs are not comparable to either the dietary NDMA intake exposures or NDMA-containing valsartan exposures, because the route of exposure is not equivalent.

136. The calculations that Dr. Madigan conducted of lifetime cumulative exposure had so many underlying assumptions and biases both within the studies themselves and within the calculations that it is unlikely that they are accurate with any degree of certainty.

Dr. Panigrahy

137. Dr. Panigrahy described his literature review process briefly. He detailed the steps for identifying the relevant animal studies, mechanistic studies, and diet and occupational epidemiology studies, as well as screening for inclusion in his review. However, he did not provide enough details, such as keywords used, for his review to be reproducible or for another person to fully critique his review. Dr. Panigrahy used Bradford-Hill criteria to assess the totality of the evidence to determine if there was a causal relationship between NDMA/NDEA and cancer.

138. Dr. Panigrahy relies heavily on animal and mechanistic evidence of cancer causation by NDMA. Of the 120 studies he identified as relevant to his review, the majority were animal, cell and tissue studies. He asserts that because similar mechanistic pathways for cancer development are found in animals and humans, experimental animal studies are valid and establish NDMA as a human carcinogen. Regulatory agencies such as IARC, NTP and others do not rely solely on animal or mechanistic evidence to classify a substance as a human carcinogen. While providing important information regarding mechanisms of action of substances, these types of studies may not reflect the manner or doses relevant to humans. An important piece of classification is epidemiologic studies of real-world exposures in humans and the risk of cancer following these exposures. Together, animal studies and human epidemiologic studies allow agencies to make determinations of grade of carcinogenicity.

139. Similar to Dr. Madigan, Dr. Panigrahy calculated lifetime cumulative exposures using the data from dietary NDMA studies that reported statistically significant increased risks of cancer to determine the levels of NDMA intake that gave rise to an increased risk of cancer. Using the NDMA level at the highest quartile of intake and assumed constant intake of NDMA at this level over 60 years to calculate the lifetime cumulative exposure. The same criticisms of Dr. Madigan's calculations apply here. NDMA intake in diet studies suffer from biases that I have described above, including recall and misclassification biases make calculations like these inaccurate. Other factors, such as the assumption of the same NDMA intake levels for 60 years of a person's life and no accounting for other sources of NDMA exposure will also likely affect the accuracy of these calculations.

140. Dr. Panigrahy relies on the rubber worker study by Hidajat (2019) as a high level of evidence for causation, calling it a well-designed study after pointing out many of the limitations of the study including no control for smoking and use of air NDMA measures, but overlooking other shortcomings such as the exposure misclassifications that may have occurred with using a job exposure matrix (JEM) and having only a single year of job information for employees to evaluate their exposures over their entire career. A job exposure matrix may lead to misclassification of subjects and their exposures especially when there is severe inter subject variability in exposures. Dr. Panigrahy uses this single study in humans with its many limitations as evidence of strength of association and dose-response for most

cancer outcomes along with animal and mechanistic studies. Without strong evidence from human studies, causation cannot be determined.

141. For stomach cancer, which has the most available human evidence, Dr. Panigrahy states that the evidence is consistent across occupational, diet and animal studies. He pointed out that of the 11 studies included in the Song meta-analysis, only four had statistically significant findings, but ignored the high heterogeneity between the studies (I^2=75.8%) reported by Song in the meta-analysis. He chose to use the pooled rate ratio reported in the meta-analysis instead of the individual studies of NDMA intake and gastric cancer as evidence of a consistent association. The individual studies show inconsistency across the 11 studies, as does the heterogeneity in the meta-analysis.

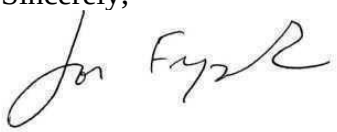
142. In his discussion of latency, Dr. Panigrahy felt that NDMA acts both as a tumor initiator and tumor promoter to activate dormant cancers. He argued that this was a biologically plausible mechanism to support carcinogenesis with short-term exposure to NDMA or NDEA, and that cancers caused by these exposures do not take a long period of time to develop. He claimed that stressful events such as carcinogen exposure, surgery, biopsy, and chemotherapy can all trigger a tumor to wake from dormancy. This argument for NDMA as a trigger fails in that all individuals are exposed to NDMA on a regular basis through diet, water, and endogenous formation. There is no way to distinguish tumor-promoting activity of dietary NDMA from NDMA in a valsartan prescription from endogenous formation of NDMA in the stomach. If NDMA exposure is a trigger for cancer growth and development, cancer incidence would be far higher in the general population and the diet studies would show much stronger effects with the daily exposure humans receive from NDMA. The studies of NDMA containing prescriptions (Gomm et al., 2021; Pottegård et al., 2018) that had short follow-up time should have seen increased risks of more cancer than just liver cancer if this were true.

The evidence I relied on do not support a link between NDMA or NDEA and cancer in humans.

143. Based on my training and experience, my review of the scientific literature, and the work conducted and outlined above, I hold the opinions expressed throughout this report to a reasonable degree of scientific certainty

144. I reserve the right to supplement these opinions as needed to reflect new information that I may receive or to respond to claims raised by other witnesses.

Sincerely,



Jon Fryzek, MPH, PhD

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